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Original article

Candidacy of adult patients with short bowel syndrome for treatment with glucagon-like peptide-2 analogues: A systematic analysis of a single centre cohort

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The corrections made in this section will be reviewed and approved by a journal production editor.

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Summary

***Background and aims*:** The glucagon-like peptide-2 (GLP-2) analogue, teduglutide, allows to reduce the intravenous supplementation (IVS) dependency of patients with short bowel syndrome and intestinal failure (SBS-IF). The rate of candidacy of SBS-IF patients for the treatment is unknown. The candidacy for teduglutide treatment of our patient cohort was investigated by a systematic analysis.

***Methods*:** The indications, contraindications, special warnings and precautions for use of teduglutide, listed in the drug monographs and in the phase-III trial protocol were adopted to categorize the patients as non-candidates (NC), potential candidates (PC) or straight candidates (SC) for the treatment. All the SBS-IF adult patients who were cured at our centre were assessed according to their clinical status on January 1st, 2020.

***Results*:** Seventy-nine patients were evaluated: 34.2% were NC due to risk of digestive malignancy, recent history of any other cancer, or listing for intestinal transplantation; 30.4% were PC, because of other premalignant conditions, risk of intestinal obstruction, entero-cutaneous fistulas, or severe co-morbidities; 35.4% were SC. The SC group showed the lowest requirement of IVS: the lowest number of days of infusion per week ($p = 0.0054$), the lowest amount of energy ($p = 0.0110$) and volume ($p = 0.0136$).

***Conclusions*:** This systematic analysis allowed a pragmatic categorization of the candidacy of patients with SBS-IF for GLP-2 analogue treatment. The SC group appeared to have the highest probability of a successful response to the treatment. A systematic analysis of SBS-IF patient candidate for GLP-2 analogue therapy would allow a homogeneous patient selection and facilitate the worldwide comparison of the results of clinical practice and research.

Keywords: Short bowel syndrome; Intestinal failure; GLP-2 analogue; Intravenous supplementation; Home parenteral nutrition; Intestinal transplantation

1 Introduction

Short bowel syndrome (SBS) is the clinical feature associated with a short bowel (SB), represented by diarrhea, fatty stools, malnutrition, and dehydration [1–3]. In adults, a SB is defined by a length of the small intestine shorter than 200 cm, measured from the duodenojejunal flexure [3]. It usually results from surgical resection of the small intestine required for the treatment of acute or chronic diseases, such as mesenteric ischemia, Crohn's disease, radiation enteritis, post-surgical intra-abdominal adhesions and post-operative complications [2–4]. In some cases, a SBS can be present notwithstanding a remnant small-bowel length >200 cm. This feature, termed “functional SBS”, can occur in conditions in which the remnant bowel function is impaired, such as in the presence of a disease or an accelerated intestinal transit [5]. SBS is the main cause of chronic intestinal failure (IF), accounting for around two-thirds of adult patients on long-term home parenteral nutrition (HPN) [5] and of patients who underwent intestinal transplantation (ITx) [6]. Chronic IF is defined as the persistent reduction of the 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” [4,5]. IVS, provided by HPN programs, is the primary and life-saving treatment for CIF [7]. After intestinal resection, SBS-IF can improve due to spontaneous intestinal adaptation and/or interventions such as diet, medication, and nontransplant surgical procedures, ending in the decrease of the IVS requirement and, in around 50% of patients, in the reversibility of SBS-IF and weaning from IVS [1,8,9].

The probability of ameliorating the outcome of SBS-IF has been increased by the introduction of therapy with the glucagon-like peptide-2 (GLP-2) recombinant analogue, teduglutide, approved in 2012 in the United States and Europe [10]. GLP-2 is a hormone secreted by enteroendocrine L cells of the distal ileum and proximal colon in response to the presence of nutrients in the gut [11]. In SBS, GLP-2 stimulates post-resection intestinal adaptation, primarily by inducing hyperplasia of small bowel mucosa and delaying gastric transit [11]. Clinical studies reported the efficacy of teduglutide, defined as the reduction of >20% of volume of the IVS requirement, in 65% of patients, 13% of whom were weaned off from IVS [12,13].

Knowing the rate of candidacy of SBS-IF patients for GLP-2 analogue treatment is a key step for planning both healthcare system resources and clinical trials. Bond et al. observed that 48% of the 152 SBS-IF patients cared at an UK national IF unit were suitable for treatment with GLP-2 analogue [14], according to the inclusion and exclusion criteria for patient enrolment in phase III randomized clinical trials (RCTs) [11,12,15,16].

The indications and the contraindications to the use of teduglutide in clinical practice are listed in the European Medical Agency (EMA) and in the US Federal Drug Administration (FDA) product monographs [17,18]. They are described in a different way from and are less detailed than those for patient inclusion in RCTs, somewhat leaving doctors to take a subjective case-by-case decision. Furthermore, the SBS-IF patient cohorts may differ among international centres, depending on the underlying diseases leading to SBS-CIF, the anatomical types of the SBS and the patients’ co-morbidities [7,14]. Therefore, a structured pathway to select patients for GLP-2 analogue treatment would allow an objective and homogeneous analysis of SBS-IF patient cohorts, thus facilitating the clinical practice and research, and the comparison among centres.

The aim of the present study was to investigate the candidacy for GLP-2 analogue treatment in the SBS-IF patients cohort cared at our centre, by a systematic analysis based on criteria derived from the EMA and FDA monographs as well as the phase III RCTs of the drug.

2 Methods

2.1 Study design and patient selection

This was a cross-sectional, observational study on patients treated at the Centre for Chronic Intestinal Failure of the S. Orsola Hospital of the University of Bologna, Italy. Patients who were on HPN for SBS-IF on January 1st, 2020 were enrolled in the study. Inclusion criterion: age ≥18 years. Exclusion criterion: presence of active malignant disease. Invasive intra-abdominal desmoid disease was included in the benign group because of the chronic nature of the condition and reflecting the fact that it is an established indication for ITx [19].

2.2 Data collection

The following data were collected as they were on January 1st, 2020, from the patients' clinical charts, which were prospectively filled out during routine clinical outpatient visits: age, gender, body mass index (BMI, kg/m^2), serum

albumin (g/L), liver function tests, type of SBS (end jejunostomy, SBS-J; jejuno-colic anastomosis, SBS-JC; jejunoileal anastomosis with an intact colon and the presence of the ileocecal valve, SBS-JIC), length of remnant SB in continuity (measured from the ligament of Treitz), percentage of remnant colon in continuity (measured according to Cumming) [20], underlying disease that required intestinal resection leading to SBS, duration of HPN treatment since the last intestinal resection, HPN program characteristics (type, volume and energy of IVS, number of days of infusion per week), type of oral diet (free food & beverage, small amount of food & beverage, only water, total fasting), basal energy expenditure (BEE), ongoing pharmacological therapy, and all the clinical and biochemical data required to evaluate the criteria for the candidacy for the treatment with teduglutide. Collected data were included in an extension of the Centre's Excel (Microsoft, 2013) file of the "ESPEN CIF Action Day" database [5,21].

Criteria to assess the candidacy for treatment with GLP-2 analogues (Table 1).

alt-text: Table 1

Table 1

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Criteria adopted in the present study for the assessment of candidacy to teduglutide treatment in adult patients with short bowel syndrome and intestinal failure (SBS-IF). The documents from which each criterion was derived are reported in brackets.

Indications
In clinical practice • Patients aged ≥18 years *(RCT-I, EMA-I, FDA-I)* • Short Bowel Syndrome dependent on parenteral support (SBS-IF) *(EMA-I, FDA-I)* • Patient stable following a period of intestinal adaptation *(EMA-I)*
Additional criteria for inclusion in RCT • SBS-IF with intravenous supplementation (IVS) ≥12 months and IVS requirement ≥3 per week *(RCT-I)*
Contraindications • Any active malignancy *(EMA-C, EMA-W&P, FDA-W&P)* • Any history of colon cancer *(RCT-E)* • Premalignant colo-rectal polyps *(RCT-E, EMA-W&P, FDA-W&P)* • History of malignancies in the GI tract and/or the hepatobiliary system including pancreas within the last 5 years *(EMA-C)* • History of any other cancer within the last 5 years *(RCT-E)* • Presence of GI premalignant condition including hepatobiliary tract and pancreas *(RTC-E, EMA-W&P, FDA-W&P)* • Radiation enteritis ongoing or the presence of damaged enteral tissue *(RCT-E)* • Celiac disease; refractory or tropical sprue *(RCT-E)* • Chronic pancreatitis *(RCT-E, EMA-W&P, FDA-W&P)*, pancreatic duct stenosis *(EMA-W&P, FDA-W&P)* • Cholecystitis *(RCT-E, EMA-W&P, FDA-W&P)* • Intestinal or other major surgery scheduled, including listing for ITx *(RCT-E)*

- Compromised immune system (e.g. AIDS, severe combined immunodeficiency), *(RCT-E)*
- Alcohol or drug addiction within the previous year *(RCT-E)*
- Major uncontrolled psychiatric illness *(RCT-E)*
- History of poor compliance with HPN therapy, including poor attendance for monitoring at HPN clinic (this was classified as three or more non-attendances or two consecutives non-attendances in the previous 12 months ∗
- Hypersensitivity or allergies to teduglutide or its excipients or tetracycline *(RCT-E, EMA-C)*

Warning and precaution conditions

- Any premalignant condition other than GI tract and/or the hepatobiliary tract and pancreas *(FDA-W&P)*
- Chronic intestinal pseudo-obstruction *(RCT-E, EMA-W&P, FDA-W&P)*
- Any strictures of the bowel *(RCT-E, EMA-W&P, FDA-W&P)*
- Active inflammatory bowel disease *(RCT-E, EMA-W&P, FDA-W&P)*
- Inflammatory bowel disease on biologics *(RCT-E)*
- Low output chronic entero-cutaneous fistulas ∗∗
- Clinically unstable concomitant diseases (e.g., cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or central nervous system), *(RCT-E, EMA-W&P, FDA-W&P)*

Special populations and dosing considerations in candidates

- Cholelithiasis *(EMA-W&P, FDA-W&P)*
- Severe hepatic impairment (Child C) ∗∗
- Chronic kidney damage categorization on the basis of eGFR (mL/min/1.73 m^2), *(EMA-S/D, FDA-S/D):*
- mild: 59-30
- moderate: 29-15
- severe: <15 or dialysis
- Concomitant oral medicinal products requiring titration or with a narrow therapeutic index *(EMA-W&P, FDA-W&P)*
- Pregnancy *(EMA-S/D)*
- Breast-feeding *(EMA-S/D, FDA-S/D)*

SBS-IF, short bowel syndrome-intestinal failure.
GI, gastrointestinal.
HPN, home parenteral nutrition.
EMA, European Medical Association [17].
FDA, Food and Drug Administration [18].
RCT, Randomized Controlled Trial [22].
EMA-I, EMA-indication.
EMA-C, EMA-contraindication.
EMA-W&P, EMA-warning & precaution.
EMA-S/D, EMA-special population and dosing consideration.
FDA-I, FDA-indication.
FDA-W&P, FDA-warning & precaution.
FDA-S/D, FDA-special population and dosing consideration.
RCT-I, RCT-inclusion criteria.

RCT-E, RCT-exclusion criteria.
∗ from Bond et al. [14].
∗∗ Authors' opinion/decision.

Criteria were derived from the indications, the contraindications, the special warnings and precautions for use, and the special populations and drug considerations listed in the EMA and the FDA product monographs of teduglutide [17,18], and from the inclusion and exclusion criteria for patients' enrollment used in the Study of Teduglutide Effectiveness in Parenteral Nutrition Dependent SBS Subjects (STEPS) [22]. In addition to the criteria derived from the above documents, the risk of poor compliance, as described by Bond et al. [14] and the presence of low output chronic entero-cutaneous (EC) fistulas were considered.

2.3 Data analysis

Based on the adopted criteria, patients were classified as "non-candidates (NC)" due to contraindications, "potential candidates (PC)" with a warning or precaution condition, or "straight candidates (SC)" for the treatment.

The term HPN described the provision of IVS, either parenteral nutrition admixture containing energy (PN) or fluids and electrolytes alone (FE). The degree of HPN dependency was categorized according to the ESPEN clinical classification of IF, consisting in eight categories, based on the type 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; FE2 or PN2, 1001–2000; FE3 or PN3, 2001–3000; FE4 or PN4, >3000 [5].

The patient's basal energy expenditure (BEE) was calculated by the Harris–Benedict equation, including the patient's ideal BW when BMI was ≥30 kg/m^2.

Kidney function was assessed by estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2 body surface) calculated by the CKD-EPI creatinine equation [23]: normal function ≥90, mildly decreased function (MDKF) 60–89, mild chronic kidney damage (CKD) 59-30, moderate CKD 29-15, severe CKD <15 or dialysis.

Intestinal failure-related liver disease (IFALD)-related cholestasis was diagnosed when conjugated bilirubin >0.3 mg/dL (>5.2 μmol/L) and total bilirubin > or <1 mg/dL (>17.1 μmol/L) [21].

Continuous variables were expressed as the median and interquartile range (IQR, 25th-75th percentiles). Categorical data were expressed as numbers (percentages). For group comparisons of categorical and continuous variables, Chi-square test and Kruskal–Wallis test were used, as appropriate. All statistical tests were two-tailed, and differences were considered significant at p-value <0.05. The Statgraphics centurion XV statistical package 2008 (StatPoint, Inc, Warrenton, VA, USA) was used for the analyses.

2.4 Ethical statement

The research was based on anonymized information included in the local file of the ESPEN "CIF database" and from the patient records. The study was approved by the Local Ethic Committee (n. 63/2017/O/Oss) and was conducted with full regard to the confidentiality of the individual patient. Voluntary informed written consent was obtained from all patients.

3 Results

3.1 Patient cohort (Table 2)

A total of 79 patients were included in the study: SBS-J 67.1%, SBS-JC 29.1%, SBS-JIC 3.8%. Four patients in the SBS-J group (7.5%) had a remnant small intestine >200 cm (functional SBS). The SBS type categories did not significantly differ for gender, age, BMI, underlying disease, and type of oral feeding.

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Table 2

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Characteristics of the cohort of patients with short bowel syndrome (SBS) and intestinal failure (IF) included in the study. Data as percentages of patients or median (interquartile range).

	Total n. 79	SBS-J n. 53	SBS-JC n. 23	SBS-JIC n. 3	p-value
Remnant bowel					
Small bowel length (cm)	70.0 (30.0–145.0)	85.0 (40.0–150.0)	55.0 (30.0–110.0)	35.0 (30.0–80.0)	0.2510
Colon length >57% (%)	22.8	0	65.2	100	
Demographic					
Males (%)	43.0	45.3	34.8	66.7	0.4888
Age (years)	60.2 (45.1–68.9)	54.8 (43.8–66.1)	65.2 (46.4–71.9)	61.6 (57.5–72.6)	0.1466
BMI (kg/m ^{2})	20.7 (18.6–22.1)	20.7 (18.7–22.3)	20.2 (17.5–21.8)	22.1 (19.7–25.2)	0.3566
BMI category (%)					0.6301
≤15	1.3	0	4.3	0	
15-18.5	22.8	22.6	26.1	0	
18.5-25	64.5	64.2	65.3	66.7	
25-30	10.1	11.3	4.3	33.3	
>30	1.3	1.9	0	0	
Underlying disease (%)					0.7737
Mesenteric ischemia	29.1	24.5	34.8	66.7	
Crohn's disease	24.0	26.4	21.7	0	
Adhesions	10.1	9.4	13.4	0	
Gardner's	7.6	9.4	4.4	0	
CIPO	6.3	9.4	0	0	
Radiation enteritis	6.3	5.7	8.3	0	
Cured cancer	5.1	7.6	0	0	
Volvulus	5.1	1.9	8.7	33.3	
Surgical complications	3.8	1.9	8.7	0	
Trauma	1.3	1.9	0	0	
Other	1.3	1.9	0	0	
Type of oral feeding (%)					0.4109
Free food & beverage	72.1	64.1	86.7	100.0	
Only water	3.8	5.7	0	0	
Small amount of food	20.2.7	24.5	13.0	0	
Total fasting	3.8	5.7	0	0	
HPN characteristics					
Duration (months)	73.2 (40.4–105.4)	61.4 (29.5–98.4)	79.4 (56.3–118.3)	64.9 (36.4–74.4)	0.2810
Day/week (n.)	7.0 (5.0–7.0)	7.0 (6.5–7.0)	6.0 (4.0–7.0)	3.0 (3.0–5.5)	0.0037
Volume/week (L)	14.0 (7.0–18.6)	15.5 (8.5-2.1)	8.5 (6.0–15.5)	3.0 (3.0–8.1)	0.0025
Volume/week/kg BW (ml)	37.5 (17.4–48.0)	38.8 (26.6–54.4)	26.3 (13.7–39.5)	7.3 (7.2–19.2)	0.0045

Energy/week (kcal)	4820 (2724–9100)	5340 (2430–9720)	4410 (2820–8040)	3300 (300–8844)	0.7633
Energy/week/kg BW (kcal)	12.5 (6.6–27.0)	13.5 (5.5–27.2)	10.9 (8.3–21.7)	8.1 (0.7–20.9)	0.6759
Energy/day (%BEE)	0.6 (0.3–1.0)	0.6 (0.3–1.1)	0.5 (0.4–0.8)	0.4 (0.0–1.0)	0.7515
IF classification (%)					0.0762
FE1	8.9	8.5	4.2	33.3	
FE2	3.8	0	0	0	
FE3	2.5	2.1	4.2	0	
PN1	15.2	8.5	29.2	33.3	
PN2	29.1	27.7	37.5	33.3	
PN3	22.8	23.4	25.0	0	
PN4	17.7	29.8	0	0	

BMI, body mass index.
BW, body weight.
CIPO, chronic intestinal pseudo-obstruction.
HPN, home parenteral nutrition.
IF, intestinal failure classification by type and volume of intravenous supplementation.
Type: PN, parenteral nutrition admixture containing energy; FE, fluids and electrolytes alone.
Volume, 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; FE2 or PN2, 1001–2000; FE3 or PN3, 2001–3000; FE4 or PN4, >3000 [Instruction: align as follows:
SBS-J, short bowel syndrome with end jejunostomy.
SBS-JC, short bowel syndrome with jejuno-colic anastomosis.
SBS-JIC, short bowel syndrome with jejunoileal anastomosis and ileocecal valve and total colon.]SBS-J, short bowel syndrome with end jejunostomy.
SBS-JC, short bowel syndrome with jejuno-colic anastomosis.
SBS-JIC, short bowel syndrome with jejunoileal anastomosis and ileocecal valve and total colon.

Statistically significant differences were observed for the HPN characteristics: the number of infusions per week and the volume and energy content were greater in SBS-J. A numerical difference was observed in the IF classification: the SBS-J group showed a higher percentage of FE-type of IVS (17.0% of patients with SBS-J vs 11.5% of patients with SBS-JC or SBS-JIC) and a lower the percentage of PN1 and PN2 (32.1% of patients with SBS-J vs 69.2% of patients with SBS-JC or SBS-JIC).

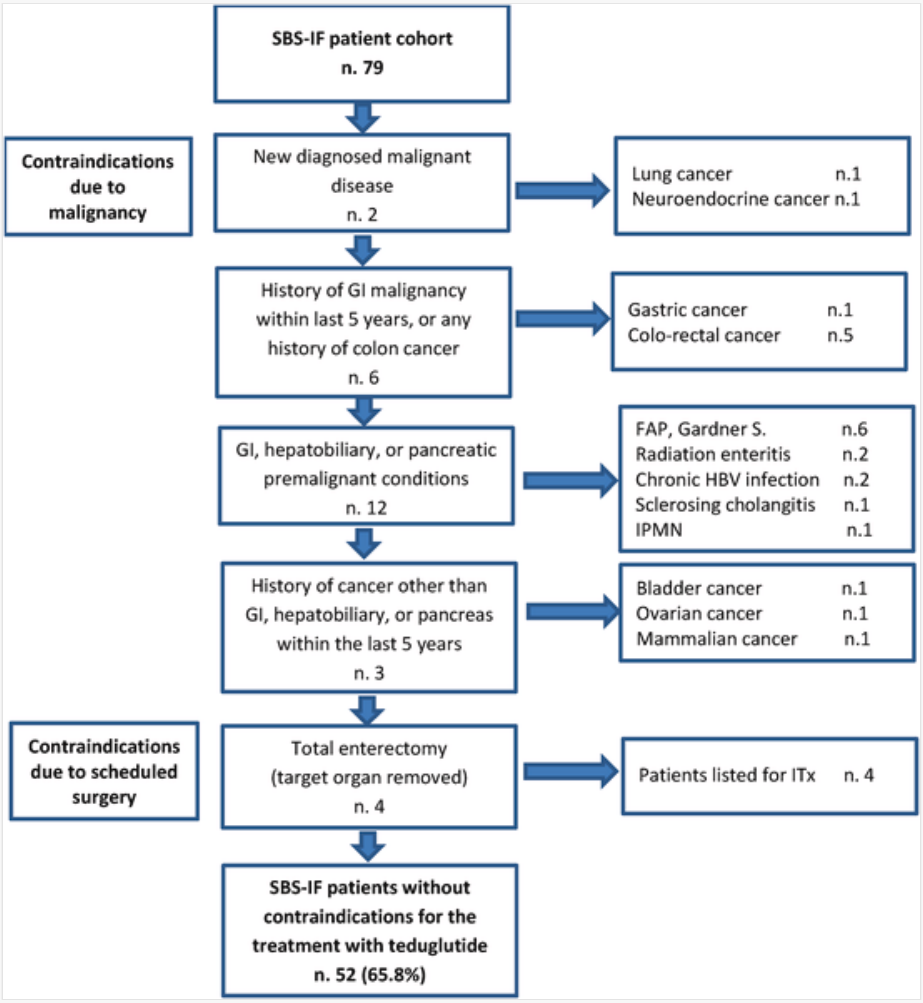
3.2 Patient's candidacy for teduglutide treatment

3.2.1 Non-candidates (Fig. 1)

Twenty-seven (34.2%) patients were NC due to contraindications to the treatment: suspicion of a new cancer, 7.4%; history of GI malignancy within last five years or any history of colon cancer, 22.2%; GI, hepatobiliary or pancreatic premalignant conditions, 44.5%; history of any other cancer within the last five years, 11.1%; total enterectomy on waiting list for intestinal transplantation, 14.8%. All but one patient had a duration of HPN ≥12 months and all had a HPN requirement ≥3 days per week.

alt-text: Fig. 1

Fig. 1



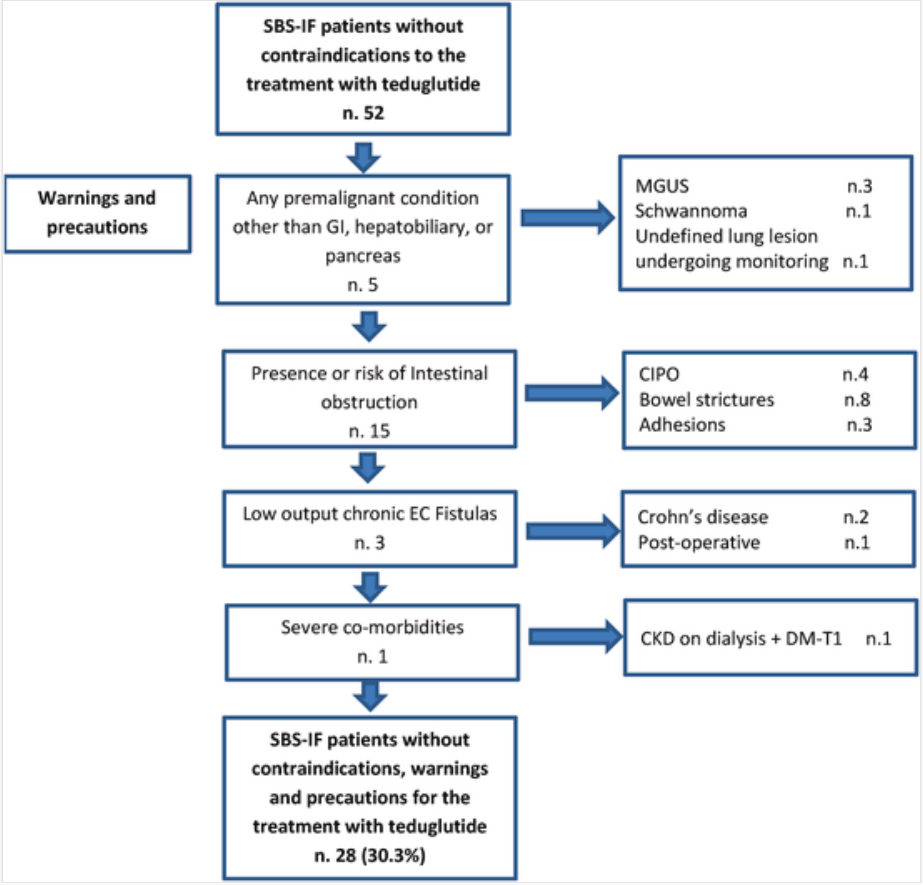
Decisional flow-chart: patients with short bowel syndrome and intestinal failure (SBS-IF) non-candidates for the treatment with teduglutide due to contraindications for the treatment.
GI, gastrointestinal; FAP, Familial adenomatous polyposis; IPMN, Intraductal Papillary Mucinous Neoplasm; ITx, intestinal transplantation.

3.2.2 Potential candidates with a warning or precaution conditions(Fig. 2)

This group was made up of 24 patients (30.4%): any premalignant condition other than GI, hepatobiliary or pancreatic, 20.8%; presence or risk of intestinal obstruction 62.5%; low output chronic EC fistulas 12.5%; severe co-morbidities 4.2%.

alt-text: Fig. 2

Fig. 2



Decisional flow-chart: patients with short bowel syndrome and intestinal failure (SBS-IF) potential candidates with a warning or precaution condition for the treatment with teduglutide.
GI, gastrointestinal; MGUS, Monoclonal Gammopathy of Undetermined Significance; CIPO, chronic intestinal pseudo-obstruction; CKD, chronic kidney disease; EC, entero-cutaneous fistulas.

All but one patient had both the clinical practice and the RCT inclusion criteria. One patient did not meet the RCTs' inclusion criteria because of IVS requirement <3 days per week.

3.2.3 Straight candidates

Twenty-eight patients (35.4%) were SC for teduglutide treatment. Fifteen (53.6%) were categorized as having a special condition or requiring drug dosing considerations: CKD was present in 6 patients (21.4%: mild, 4; moderate, 1; severe, 1), cholelithiasis in 9 (32.1%) and treatment with warfarin in 4 (14.3%).

All but one patient had both the clinical practice and the RCT inclusion criteria. One patient did not meet the RCTs' inclusion criteria because of IVS requirement <3 per week.

3.3 Comparison between straight candidates, potential candidates, and non-candidates for the treatment with teduglutide (Table 3)

The SC group had a statistically significant lower requirement of HPN represented by lower number of days of infusion per week as well as lower IVS energy and volume per day. This was represented by the highest percentages of FE (17.9%) and of PN1 and PN2 (18.5%) in the IF clinical classification categories.

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Table 3

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Comparison between patients with short bowel syndrome (SBS) and intestinal failure (IF) categorized as straight candidates, potential candidates, or non-candidates for the treatment with teduglutide. Data as percentages of patients or median (interquartile

range).

	Straight Candidates n. 28	Potential candidates n. 24	Non-candidates n. 27	p-value
SBS type *(%)*				0.6763
SBS-J	60.7	62.5	77.8	
SBS-JC	35.7	33.3	18.5	
SBS-JIC	3.6	4.2	3.7	
Remnant bowel				
Small bowel length (cm)	70.0 (37.0–115.0)	77.5 (47.5–150.0)	80.0 (20.0–150.0)	0.6998
Colon length > 57% (%)	28.6	20.8	18.5	
Demographics				
Male (%)	50.0	45.8	33.3	0.4345
Age (years)	61.7 (52.6–69.3)	49.4 (37.9–69.3)	57.5 (46.4–67.8)	0.6494
BMI ($kg/m^{2,}$)	21.4 (19.0–24.5)	20.3 (18.6–22.1)	20.1 (17.3–22.1)	0.1355
BMI category *(%)*				0.2540
≤ 15	0	0	3.7	
15-18.5	21.4	20.8	25.9	
18.5-25	57.2	75.0	63.0	
25-30	21.4	4.2	3.7	
> 30	0	0	3.7	
Underlying disease *(%)*				0.0002
Mesenteric ischemia	42.9	8.3	33.4	
Crohn's	32.1	33.3	7.4	
Adhesions	10.7	16.8	3.7	
Gardner's	0	0	22.2	
CIPO	0	20.8	0	
Radiation enteritis	0	12.5	7.4	
Cancer	0	0	14.8	
Volvulus	3.6	8.3	3.7	
Surgical complications	10.7	0	0	
Other	0	0	3.7	
Trauma	0	0	3.7	
Oral feeding *(%)*				0.0006
Free food & beverage	96.4	50.0	66.7	
Only water	0	4.2	7.4	
Small amount of food	3.6	45.8	14.8	
Total fasting	0	0	11.1	
HPN characteristics				
Duration (months)	78.5 (48.6–103.4)	80.0 (41.6–143.3)	45.0 (18.5–86.0)	0.0532

Day/week (n.)	5.5 (3.5–7.0)	7.0 (5.2–7.0)	7.0 (7.0–7.0)	0.0067
Volume/week (L)	7.3 (5.2–14.1)	14.0 (8.5–18.0)	16.4 (10.5–24.5)	0.0057
Volume/week/kg BW (ml)	18.8 (13.3–37.4)	39.1 (27.1–46.2)	44.6 (32.8–65.1)	0.0012
Energy/week (kcal)	3139 (2335–4948)	7560 (3546–9374)	5440 (3648–11,760)	0.0108
Energy/week/kg BW (kcal)	8.1 (5.4–12.2)	20.8 (10.7–27.2)	15.8 (9.4–31.0)	0.0034
Energy/day (%BEE)	36.0 (25.9–54.8)	92.8 (42.8–107.4)	62.2 (45.2–137.8)	0.0051
IF classification *(%)*				0.0421
FE1	14.3	0	11.1	
FE2	0	4.2	7.4	
FE3	3.6	4.2	0	
PN1	25.0	16.7	3.7	
PN2	35.7	37.4	14.8	
PN3	7.1	29.2	33.3	
PN4	14.3	8.3	29.6	
eGFR (*ml/min/1.73 m* ^{2})	80.5 (55.5–98.5)	81.0 (65.0–108.5)	70.5 (50.0-70-0)	0.2976
Albumin (g/L)	38.8 (36.5–40.3)	37.0 (35.0–39.9)	39.0 (36.2–42.0)	0.2814
Total bilirubin (mg/dL)	0.6 (0.4–1.0)	0.7 (0.5–1.0)	1.0 (0.8–1.7)	0.0314
Direct bilirubin (mg/dL)	0.2 (.1–0.3)	0.2 (0.1–0.3)	0.3 (0.2–0.4)	0.0340
INR	1.1 (1.1–1.3)	1.2 (1.1–1.3)	1.1 (1.1–1.3)	0.3590
GGT (U/L)	37.5 (14.5–68.5)	44.0 (22.0–87.0)	69.0 (43.0–152.0)	0.0288
ALP (U/L)	115.5 (89.0–154.0)	144.0 (93.0–197.0)	121.0 (102.0–170.0)	0.5763
ALT (U/L)	32.5 (21.0–41.5)	28.0 (23.5–41.5)	40.0 (27.0–52.0)	0.2167
AST (U/L)	30.5 (23.0–36.0)	30.0 (24.0–39.0)	33.5 (27.0–47.0)	0.3449
Gallbladder stones *(%)*	32.1	25.0	14.8	0.3204
Renal stones *(%)*	35.7	12.5	7.4	0.0174
Cardiac pathology *(%)*	14.3	25.0	11.1	0.3807
Other diseases *(%)*	14.3	25.0	14.8	0.5339
CKD category *(%)*				0.9224
≥90	71.4	79.2	63.0	
89-60	7.1	4.2	14.8	
59-30	14.3	12.5	14.8	
29-15	3.6	0	3.7	
< 15	3.6	4.2	3.7	
IFALD-Cholestasis *(%)*				0.1565
Conjugated bilirubin > 0.3 mg/dL	10.7	0	7.7	
Conjugated bilirubin > 0.3 mg/dL and total bilirubin > 1 mg/dL	14.3	25.0	38.5	

ALT, alanine aminotransferase.
ALP, alkaline phosphatase.

AST, aspartate aminotransferase.
BMI, body mass index.
BW, body weight.
CIPO, chronic intestinal pseudo-obstruction.
CKD, chronic kidney disease categories by eGFR (ml/min/1.73 m^2).
GGT, gamma-glutamyl transferase.
HPN, home parenteral nutrition.
IF, intestinal failure classification by type and volume of intravenous supplementation.
Type: PN, parenteral nutrition admixture containing energy; FE, fluids and electrolytes alone.
Volume, 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; FE2 or PN2, 1001–2000; FE3 or PN3, 2001–3000; FE4 or PN4, >3000 [Instruction: align as follows
IFALD, intestinal failure associated liver disease.
INR, prothrombin international normalized ratio.
SBS-J, short bowel syndrome with end jejunostomy.
SBS-JC, short bowel syndrome with jejuno-colic anastomosis.
SBS-JIC, short bowel syndrome with jejunoileal]SBS-J, short bowel syndrome with end jejunostomy.
IFALD, intestinal failure associated liver disease.
INR, prothrombin international normalized ratio.
SBS-JC, short bowel syndrome with jejuno-colic anastomosis.
SBS-JIC, short bowel syndrome with jejunoileal anastomosis and ileocecal valve and total colon.

The SC group also showed a statistically significant higher frequency of free oral diet and of renal stones, and a lower serum concentrations of liver function tests as well as a numerically lower percentage of IFALD-cholestasis.

The three groups did not significantly differ in gender, age, BMI and SBS type. The group of NC showed numerical higher percentages of female and of underweight patients (BMI<18.5 kg/m^2), and a lower percentage of SBS with a colon.

4 Discussion

This is the first report on the candidacy of SBS-IF patients for treatment with GLP-2 analogues assessed by a systematic analysis, based on criteria derived from the product monographs [17,18] and the phase III RCT of teduglutide [22]. According to the product monographs' indication criteria, in our SBS-IF cohort, one-third of patients was SC for the treatment, one third was PC with warning and precaution conditions and one third was NC because of contraindications to the treatment. Furthermore, one-half of the SC group had a special condition or required drug dosing considerations. One patient in each group did not meet the RCTs' inclusion criteria, because of IVS requirement <3 days per week or a duration of HPN <12 months. Thus, the candidacy rate for RCTs could be lower than that for clinical practice, because of the obvious more restrictive criteria for inclusion in RCTs. Indeed, the clinical practice refers to the product monographs, where the indication criteria are generically defined as “dependency on IVS” (both EMA and FDA), and “patient stability following a period of intestinal adaptation” (EMA), allowing the physician a wider range of case-by-case decisions. The candidacy rate for the treatment was related to the underlying disease and the patient's co-morbidities. Since the case-mix of patients with SBS-IF can differ among the IF centres, the percentages of suitability for the treatment can differ as well. SBS-IF due to mesenteric ischemia (MI) or to Crohn's disease (CD) accounted for 53.1% (MI 29.1%, CD 24.0%) of our cohort, 58.0% (MI 20.5%, CD 37.5%) of the Manchester cohort in UK [14], 59.4% (MI 35.0%, CD 24.40%) of the Ringhospitalet cohort in Denmark [24] and 49.0% (MI 43.0%, CD 6.0%) of the Clichy cohort in France [25]. Equally, MI and CD were the most frequent underlying diseases among the SBS-IF patients who were considered candidates to the treatment. The French multicenter real-world experience on teduglutide showed that SBS-IF due to MI or CD were the 69.0% (MI 39.0%, CD 30.0%) of the total cohort [26]. They accounted for 59% (MI 44%, CD 15%) in the German cohort [27] and for 86% (MI 34%, CD 52%) among the UK cohort [14]. Similarly, they represented 75.0% of our SC to the treatment, whereas they were only the 40.7% of NC and 41.6% of PC. Also the frequency of colon-in-continuity in the candidate groups differed between the centres: 39.3% in our centre, 65.0% in the French cohort [26], 19.3% in the UK cohort [14], and 78% in the German cohort [27]. In comparison with our study, Bond et al., who applied the STEPS selection criteria, reported a higher frequency of candidates to the treatment (48.0% vs 34.6%) [14]. This difference could be due to both the characteristics of the case-mix of the two patient cohorts and the criteria adopted for the assessment of patient suitability. Overall, these data indicate that a systematic analysis of candidates to GLP-2 based on agreed criteria would allow a homogeneous assessment of candidacy, thus facilitating the comparison of results of clinical practice and research.

The presence or the risk of malignancy, conditions that could put the patient in undue risk or compromise the good outcome of the treatment, and a scheduled major surgery, including listing for ITx were the contraindication criteria for the treatment. Based on the pharmacologic activity and findings in animals, teduglutide has the potential to cause hyperplastic changes including neoplasia [18]. The effects of GLP-2 are mediated by the activation of a G-protein-coupled transmembrane receptor (GLP-2R), that is expressed in the GI tract and central nervous system. In GI tract, GLP-2R was localized in enteric neurons, enteroendocrine cells, and myofibroblasts, but not in epithelial cells. GLP-2 stimulates intestinal growth through secondary mediators, such as insulin like growth factor (IGF-I), epidermal growth factors (ErbB ligands), and β-catenin, and through the involvement of Akt phosphorylation, which are considered hallmarks of tumorigenesis [28]. A study examined GLP-2R expression in different GI tumors (such as colorectal adenocarcinomas, gastric adenocarcinomas, and stromal tumors) and extra-GI tumors (such as small cell lung cancers, rhabdomyosarcomas, and leiomyosarcomas) [29]. Expression of GLP-2R messenger RNA (mRNA) was observed in 68% gastrointestinal stromal tumors (GIST) [29], in four of four ileal carcinoid tumors and in two of seven colon adenocarcinomas. A systematic review reported that teduglutide treatment for up to 30 months did not increase risk in patients without any known preexisting cancer and promoted growth of pre-existing neoplasia in rodents [30]. A post hoc analysis of the STEPS studies showed that colonic polyps were present in 12% of 73 patients who underwent the baseline colonoscopy, and in 9 (18%) of 50 patients who underwent postexposure colonoscopy [31]. In these 9 patients, polyps were detected in 3 patients who had polyps removed at the baseline colonoscopy. The duration of teduglutide exposure at the time of polyp discovery in the nine patients ranged from 8 to 36 months. Histological analyses in 7 patients reported no evidence of malignancy or high-grade dysplasia; various adenomas were reported in 5 patients. In RCT/extension teduglutide studies, including 173 patients for a total of 222 person-years exposure to the drug, colonic polyps, rectal polyps and small intestinal polyp were reported in 1.7%, 1.2%, and 0.6% of patients, respectively [32]. Furthermore, 3 events of cancer were observed, one GI adenocarcinoma, considered drug-related, and 2 lung cancers, not considered drug-related [32]. Case reports of de novo development of duodenal and small intestinal polyps in patients who were not considered at increased risk [33,34], accelerated colorectal polyposis in an immunosuppressed patient with a small bowel transplant [35], and aggressive growth of duodenal and rectal adenomas in patients with familial adenomatous polyposis [36] were reported. The development of extra-GI tumors, an alveolar rhabdomyosarcoma of the nasopharynx [37], and a recurrence of a squamous cell skin carcinoma [38], was reported in two patients who were on teduglutide treatment, but a relationship with the drug was not proved. The risk of malignancy is listed in the warning and precaution section of the Gattex® monograph [18]. Any history of cancer within the last 5 years is listed as exclusion criteria in the STEPS study protocols [22]. Active or suspected malignancy and a history of malignancies in the gastrointestinal tract, including the hepatobiliary system and pancreas within the last five years are contraindications to the treatment in the Revestive® monograph [17]. We expanded the list of malignancy-related contraindications including any history of colon cancer, a history of any cancer within the last 5 years and the presence of any premalignant condition of the GI, hepatobiliary system and pancreas.

Concerning the presence of any GI premalignant condition, in addition to intestinal polyps, we included chronic radiation enteritis, sclerosing cholangitis, IPMN and chronic virus-C hepatitis, all conditions at increased risk of malignancy. However, excepting the report on FAP [36] and one patient with radiation enteritis in the Lam et al. cohort [39], no studies on patients with the other conditions treated with teduglutide are present in the literature. We considered contraindications to the treatment also the presence of chronic pancreatitis, pancreatic duct stenosis, and cholecystitis. In fact, although these conditions are considered as warning and precaution conditions both for EMA and FDA, they have been reported as adverse event in clinical studies [17] and as exclusion criteria in STEPS [22]. Furthermore, teduglutide has been reported to increase lipases and/or amylases levels depending on the drug dosage [40–42]. The appropriateness of our expansion of the list of absolute contraindications including any history if GI cancer independently of the time lapsed wince its healing, of any cancer other than GI in the 5 years before, of any GI premalignant condition, and the presence of active pancreatic and biliary non-malignant disease could be considered a matter of debate.

One-third of our patients were PC with warning and precaution conditions, such as any premalignant condition other than GI, CIPO and any strictures of the bowel, active IBD and IBD on biologics, low output chronic EC fistulas, and clinically unstable concomitant diseases that could have compromised the good outcome of the treatment. Treating with GLP-2 analogues patients with SBS-IF with these conditions requires a high level of care by an expert multidisciplinary team and is a challenging task because of the lack of published data. It is not known if premalignant conditions other than GI tract and hepatobiliary-pancreatic system, such as Monoclonal Gammopathy of Undetermined

Significance, or Schwannoma, could actually be at increased risk for accelerated cancer development under treatment with GLP-2 analogues. The presence of a risk of intestinal occlusion due to intra-abdominal adhesion requires a close monitoring. No data are available about the treatment with GLP-2 analogues in patients with CIPO who undergo extensive intestinal resection ending in SBS-J with a very short small bowel remnant. Concerning IBD, patient with active CD on biologic therapy were excluded from the STEPS [22]. At the moment, only a few papers have been published about treating with teduglutide patients with active IBD on biologics [38,41,43,44]. So far, the results have not indicated any association with GLP-2 analogue and worsening of IBD or other related side effects. On the contrary, many studies suggest the potential anti-inflammatory effect of GLP-2 [45]. We did not, therefore, preclude the patients from the treatment, notwithstanding the need of a careful case-by-case evaluation of the status of the underlying disease. No data are available on low output EC fistulas. In the literature, we only found that Buchman et al. considered as a contraindication the presence of more than 3 external fistulas [38]. As a result, this is an area of major uncertainty and of clinical and ethical debate, that requires a case-by-case decision and warrants of an expert consensus.

The comparison of the three groups of our patient showed that those who were deemed to be SC for the GLP-2 analogue treatment had the lowest requirements of IVS, thus having the highest probability of a successful result either as reduction of IVS requirement or weaning off. This would imply that a systematic pathway of patient selection would allow to choose those patients with the highest probability of a successful treatment, although some of them were classified as special populations or as needing dosing considerations, because of cholelithiasis, CDK, or concomitant oral medicinal products requiring titration or with a narrow therapeutic index.

5 Conclusions

This systematic analysis of candidacy of patients with SBS-IF for GLP-2 analogue treatment, based on the indication, contraindication and warnings criteria listed in the drug monographs and in the RCT protocols allowed a pragmatic categorization of the patient cohort as NC, PC and SC. The SC group had the lowest IVS requirements and appeared to have the highest probability of a successful response to the treatment. A systematic analysis of SBS-IF patient candidate for GLP-2 analogue therapy would allow HPN/IF centres to make a homogeneous patient selection and would facilitate the worldwide comparison of the results of clinical practice and research.

Author contribution

LP, ASS, FMV concepted and designed the study, interpreted the data and revised the manuscript.

ASS, FMV, AM, CP and MG acquired and interpreted the data and drafted the article.

All the Authors approved the final version of the article before submission.

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Conflict of interest

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ASS, FMV, AM, CP and MG have no conflict of interest to declare.

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The corrections made in this section will be reviewed and approved by a journal production editor. The newly added/removed references and its citations will be reordered and rearranged by the production team.

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Highlights

- Short bowel syndrome with intestinal failure (SBS-IF) needs intravenous nutrition.
- Intestinal rehabilitation therapy may allow weaning from intravenous nutrition.
- The GLP-2 analogue, teduglutide, facilitates intestinal rehabilitation in SBS-IF.

- The rate of candidacy for treatment with GLP-2 analogues is unknown.
- A systematic analysis of SBS-IF patients for GLP-2 candidacy was developed.
- ~~This will~~ to homogenize the worldwide selection of SBS-IF patients for GLP-2 analogue treatment.

Q1