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## Glucagon-like peptide-2 analogues for Crohn's disease patients with short bowel syndrome and intestinal failure

Marco Pizzoferrato, Pierluigi Puca, Sara Ennas, Giovanni Cammarota, Luisa Guidi

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### Abstract

Short bowel syndrome (SBS) with intestinal failure (IF) is a rare but severe complication of Crohn's disease (CD), which is the most frequent benign condition that leads to SBS after repeated surgical resections, even in the era of biologics and small molecules. Glucagon-like peptide-2 analogues have been deeply studied recently for the treatment of SBS-IF. These drugs have a significant intestinotrophic effect and the potential to reduce the chronic dependence of SBS-IF patients on parenteral support or nutrition. Teduglutide has been approved for the treatment of SBS-IF, and apraglutide is currently in clinical development. The use of these drugs was examined with a focus on their use in CD patients.

**Key Words:** Short bowel syndrome; Intestinal failure; Crohn's disease; Glucagon-like peptide-2 analogues; Teduglutide; Apraglutide; Glepaglutide

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**Core Tip:** Short bowel syndrome with intestinal failure and chronic dependency on parenteral support are rare but severe complications of Crohn's disease (CD) after repeated intestinal resections. New therapeutic options are available, including glucagon-like peptide-2 analogues. Their use in CD appears safe and efficacious, but more data from specifically designed studies are needed.

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## INTRODUCTION

Short bowel syndrome (SBS) in adults is a condition in which the normal length of the bowel (which ranges from 3 to 8 metres) is reduced to less than 2 metres[1]. It is classified anatomically into: (1) Type 1: End-jejunostomy; (2) Type 2: Jejunocolonic anastomosis; and (3) Type 3: Jejunoleal anastomosis[2]. The onset of SBS may lead to intestinal failure (IF), which is defined according to the European Society for Clinical Nutrition and Metabolism as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, and intravenous supplementation is required to maintain health and/or growth. A reduction in gut absorptive function that does not require intravenous supplementation to maintain health and/or growth is considered intestinal deficiency. IF is categorised according to temporal and functional evolution into: (1) Type 1 - acute, short term and self-limiting; (2) Type 2 - a prolonged acute condition, often in metabolically unstable patients, that requires complex multidisciplinary care and intravenous supplementation over periods of weeks or months; and (3) Type 3 - a chronic condition in stable patients[3].

However, not all patients with SBS develop IF, and not all patients with IF have underlying SBS[1]. The anatomical classification of SBS is mirrored by different clinical presentations: (1) Type 1 (end-jejunostomy with no colon in continuity) shows a higher risk of dehydration and electrolyte imbalance, especially immediately after surgical resection; (2) Type 2 (jejunocolonic anastomosis) patients may develop malnutrition in a long-term setting (months to years); and (3) Type 3 (jejunoleal anastomosis with ileocaecal valve conservation) has a lower risk of malnutrition[4].

The causes of SBS-IF in 2919 patients with benign chronic IF were CD (22.4%), mesenteric ischaemia (17.7%), surgical complications (15.8%), primary chronic pseudo-obstruction (9.75%) and radiation enteritis (7.3%). The pathogenetic mechanisms of IF were heterogeneous in the same population, with most patients presenting (38.6%) with end jejunostomy, and approximately 20% of patients presenting with jejunocolonic anastomosis[5]. The remainder of the cohort was divided into intestinal dysmotility (17.5%), fistulas (7%), mucosal disease (6.8%), jejunoleal anastomosis (5.9%), and mechanical obstruction (4.4%)[5]. However, other reports, such as the United States intestinal transplant (IT) registry, describe mesenteric ischaemia as the first cause of IT (24%) and CD as the second most frequent cause (11%)[6].

Following a large bowel resection, humans undergo a wide range of functional and anatomical modifications due to the reduction of the intestinal area dedicated to the absorption of nutrients[7]. Structural and anatomical changes include crypt hyperplasia, angiogenesis, bowel dilation and bowel elongation. Functional changes include accelerated crypt differentiation, a slower transit time, an increase in the number of transporters and a consequent increase in nutrient absorption[8]. After an early phase immediately following surgery, the adaptation phase starts 48 h after resection and lasts at least 1-2 years. Most of the intestinal adaptation described above occurs in this phase. Nutritional homeostasis may be achieved in the maintenance phase *via* oral autonomy or with parenteral support (PS)[3].

The clinical consequences of SBS are very heterogeneous and may considerably impact the patient's quality of life. One frequent symptom is diarrhoea due to accelerated intestinal transit, intestinal and gastric increased secretion[9], intestinal bacterial overgrowth[10], and the malabsorption of fats and bile salts[11,12]. One common consequence of SBS is the formation of stones. Asymptomatic gallbladder stones were reported in a population of SBS patients[13]. Most of these stones consist of calcium bilirubinate. The formation of gallbladder stones is favored by altered enterohepatic circulation[14], gallbladder hypomotility[15], and the reduced secretion of cholecystokinin after meals[16]. The formation of calcium oxalate kidney stones is also common, especially in patients with SBS and colon in continuity[17]. Within the colon, unabsorbed long-chain fatty acids compete with oxalate for available luminal calcium, and a larger amount of free oxalic acid is absorbed *via* passive diffusion and ultimately excreted by the kidney[13]. Other mechanisms may be involved, such as regional differences in oxalate absorption[17].

A relatively rare but underestimated complication of patients with SBS, especially patients with colon preservation, is so-called D-lactic acidosis. When a carbohydrate meal is consumed, colonic bacteria metabolise non-absorbed carbohydrates to short-chain-fatty acid and lactate. Lactate lowers the intraluminal pH, which leads to the overgrowth of D-lactate-producing bacteria, *Bifidobacterium* and *Lactobacillum*. D-lactate is absorbed into the systemic circulation and is responsible for the onset of neurological symptoms[18]. From a clinical point of view, this condition is characterized by neurological symptoms, such as ataxia, movement disorders and altered mental status[19].



The prevalence of IF due to benign disease ranges from 5 to 80 cases of patients on chronic home parenteral nutrition (HPN) per million population in Europe[3]. Benign chronic IF and secondary SBS are in the directory of rare diseases ORPHANET (ORPHA:294422 and ORPHA:95427).

## SBS-IF IN CROHN'S DISEASE

A survey in 64 centres from 22 countries enrolling 2919 patients on HPN described CD as the most frequent benign cause of SBS-IF[5]. However, a long-term study from a single IF centre in the United Kingdom described a change in the causes of IF over time, and the prevalence of CD decreased from 44% in 1978-1988 to 22% in 2006-2012[20].

Surgery remains a common treatment for CD during the course of the disease[21]. The indications for small intestinal resection in CD range from complications, such as stenosis, fistulas and abscesses, to the treatment of medically refractory disease[22]. Surgery rates in CD declined in recent decades due to multifactorial reasons, including earlier diagnosis and treatment, the use of biological agents, a decline in smoking rates, and improved patient education[23,24].

Although a United States population study demonstrated that biological agents reduced the proportion of CD patients undergoing resection, this reduction was not observed in patients with SBS-IF, which likely represents a subgroup of CD patients characterized by a more severe disease course and resistance to treatments[25]. Predictors of SBS-IF in CD were reviewed and roughly correspond to predictors of severe disease course. Notably, the CD phenotype characterized by an ileocolonic location is associated with a greater risk, and the absence of the ileocecal valve increases the risk of HPN dependence. Patients with perianal disease at diagnosis have a higher risk of disabling disease course, including bowel resections, and patients with penetrating disease have longer bowel resections and more frequently depend on HPN. Patients younger than 40 years at the time of CD diagnosis were more likely to have a "very short bowel" (< 100 cm), and an older age at first surgery was associated with decreased odds of IF. Patients who had ever smoked were more likely to develop IF. A family history of inflammatory bowel disease (IBD), frequent corticosteroid use for flares, and the number of bowel resections and complications of surgery were also identified as risk factors for SBS-IF[26].

A recent case-control study of 410 CD patients (41 with SBS) at a single centre demonstrated that subjects with SBS underwent significantly more bowel resections than controls. Patients treated with IV steroids were at higher risk of SBS, and Montreal B1 (inflammatory) behavior and treatment with budesonide characterized patients at a lower risk of SBS[27].

Another study of 2456 IBD patients identified 25 patients who required long-term HPN (1%, 24 CD). They described that HPN use was significantly associated with smoking, narcotic use, IBD-related surgeries, and lower quality-of-life scores. They found that these refractory patients had a 15-fold increase in annual median health care charges compared to control IBD patients[28].

## MEDICAL TREATMENT OF SBS-IF AND COMPLICATIONS

The management of SBS-IF is complex, expensive and requires a multidisciplinary approach. A multidisciplinary team consisting of at least gastroenterologists, nutritionists, surgeons, radiologists, stoma therapists, care managers, pharmacists, and home care nurses is useful to provide patients with the best management possible[29]. The process of intestinal rehabilitation may be improved with medical management and includes spontaneous adaptation (dietary intervention and oral rehydrating solutions) and pharmacological therapies to improve symptoms. Gastric hypersecretion may be reduced with Proton-pump inhibitors. The accelerated transit time may be slowed with loperamide. The reduced reabsorption of bile acids may be targeted with cholestyramine, and bacterial overgrowth may be modulated with antibiotics, particularly rifaximin. Other drugs commonly used in the symptomatic management of diarrhoea are diphenoxylate, atropine, codeine, and antihistamines (*e.g.*, ranitidine and cimetidine).

Although symptom management provides an initial benefit in quality of life and the patient's perception of disease, it does not provide any improvement in prognosis[30]. The cornerstone in the treatment of SBS-IF is HPN. HPN ensures the correct intake of micro- and macronutrients and provides a significant improvement in prognosis. HPN is a life-saving treatment for these patients, but it significantly lowers patients' quality of life and is not free of complications[31].

HPN is generally administered in a single dose *via* a nutrition bag and infused over 10 to 12 h, typically overnight. Patients are encouraged to continue oral feeding with HPN[32]. Catheter infections [also called catheter-related blood stream infections (CRBSIs)] and central venous catheter (CVC) thrombosis are the most feared complications of parenteral nutrition. The rates of CRBSI range from 0 to 11.89 episodes per 1000 catheter days in systematic reviews and meta-analyses[33]. No significant difference was shown in catheter infection rates between peripherally inserted central catheters (PICCs) and tunneled catheters. However, PICCs showed lower CRBSI rates than ports[34]. The more frequently implicated pathogens are Gram-positive bacteria (*Staphylococcus aureus*, *Enterococcus species*, and *Strepto-*

*coccus species*), Gram-negative bacteria (*Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacter cloacae*), and fungi (*Candida parapsilosis*, *Candida albicans*, and *Candida glabrata*)[35]. Antibiotic therapy is the mainstay of CRBSI management. An empiric regimen with broad-spectrum drugs is generally used until the responsible agents are identified[36]. Bacterial infections are generally treated with the catheter in place, but fungal infections are treated by removing the catheter[37]. Locking the catheter with ethanol[38,39], taurolidine[40] or antibiotics[41] has been proposed as a strategy for the prevention of CRBSI. However, the results from randomized controlled trials (RCTs) are nonunivocal, and no clear guidelines have been generated on this topic[42].

The incidence of CVC thrombosis is approximately 0.12 events/1000 catheter days[43]. The management of catheter-related thrombotic events is based on the administration of low-molecular-weight heparins (LMWH)[44] or thrombolytic agents, such as streptokinase[45]. Flushing the CVC with a saline solution or LMWH has been proposed as a measure to prevent the occurrence of thrombotic events[46,47].

One possible complication of HPN is progressive steatohepatitis and liver damage, also known as “IF-associated Liver Disease” (IFALD). Up to half of the patients receiving total parenteral nutrition develop severe liver disease after 5 years[48,49], and higher rates of incidence and prevalence are observed in children[50]. IFALD manifests as steatosis, steatohepatitis or a cholestatic pattern. It may lead to progressive liver damage with fibrosis and cirrhosis in some cases[51]. Therapeutic strategies include fish oil-based lipid emulsions[52], ursodeoxycholic acid[53], and lecithin administration[54].

Malabsorption-related anaemia may develop into microcytic anaemia due to iron deficiency or macrocytic anaemia due to malabsorption of vitamin B12 and folate, which lead to the need for iron and vitamin supplementation[3,55]. The occurrence of metabolic bone disease must be monitored[56]. Bone densitometry, the biochemical dosing of vitamin D and calcium profiles play a role in preventing the insurgency of metabolic bone disease[57]. Manganese toxicity must be noted. Manganese is a central element of HPN, but its requirement is low. This low requirement leads to an increase in blood concentration and accumulation in the central nervous system, which is detectable using magnetic resonance imaging. Manganese toxicity presents with neurological symptoms that are similar, but not identical, to Parkinson’s disease[58].

## NEW THERAPIES: GLUCAGON-LIKE PEPTIDE-2 ANALOGUES

Hormonal manipulation may also increase intestinal absorption[59] (Figure 1). Only two molecules have been approved for SBS-IF therapy, growth hormone in the United States and the glucagon-like peptide-2 (GLP-2) analogue teduglutide (TED) in the United States and Europe[60,61]. TED is a recombinant analogue of GLP-2 that is resistant to degradation by DPP4. The elimination half-life of TED is 2 to 6 h, which allows administration as a daily subcutaneous injection. Notably, the elimination half-life of endogenous GLP-2 is approximately 7 min[62].

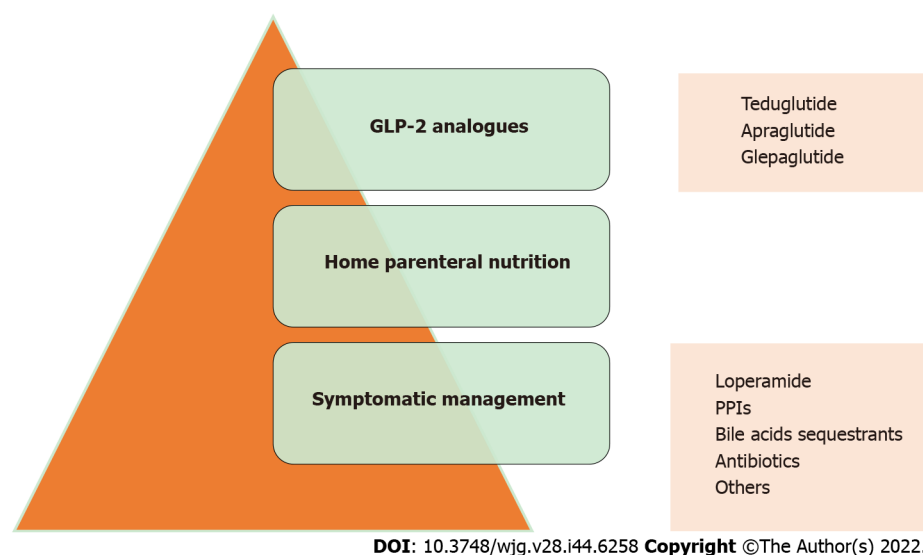
The mechanism of action of TED is complex and involves direct and indirect effects of interaction with a GLP-2 receptor and includes the following most relevant factors: Crypt cell proliferation, increase in bowel weight and villous growth, enhancement of intestinal barrier function, inhibition of motility of the gastrointestinal tract and gastric acid secretion, and increase of intestinal blood flow[60]. The effect of TED on intestinal epithelial stem cells is of particular relevance in the possible risk of the drug being tumorigenic[63].

The first open-label trial on TED was performed and published in 2005. Sixteen patients with end-jejunostomy or colon in continuity received s.c. TED for 21 d. Patients treated with TED showed an increased absorption of nutrients, urine output and sodium excretion. TED significantly increased villus height, crypt depth and mitotic index in the small intestines of patients with end-jejunostomy. Leg oedema and enlargement of the stoma nipple were the most common, but not severe, side effects[64].

The most significant RCT of TED effectiveness was performed from 2008 to 2011 and published in 2012 (STEPS study). Eighty-six patients receiving PS were enrolled: 43 patients underwent management with TED, and 43 were treated with placebo (PBO) for 24 wk. In the TED group, 63% of patients were responders who reduced their PS by at least 20% compared to 30% of patients in the PBO group ( $P = 0.02$ ). The secondary outcomes of this study were the reduction of parenteral nutrition volume at week 24 (2.1 litres per week difference between the TED group and PBO,  $P < 0.05$ ) and the number of patients achieving at least 1 d off parenteral nutrition per week (21/39 in the TED group *vs* 9/39 in the PBO group)[65].

The STEPS study was followed by STEPS-2, which was a 2-year, open-label extension of the prior study. The enrolled patients completed 24 wk of TED (TED/TED) or PBO (PBO/TED) in the initial PBO-controlled study or qualified for the original study but were not treated (NT/TED) because of full enrolment. Patients received 0.05 mg/kg/d subcutaneous TED for up to 24 mo (NT/TED and PBO/TED) or up to 30 mo (TED/TED). In patients who completed the study, clinical response (as defined in the STEPS study) was achieved in 28/30 (93%) TED/TED, 16/29 (55%) PBO/TED, and 4/6 (67%) NT/TED patients. The mean PS volume reductions from baseline were 7.6 (66%), 3.1 (28%), and 4.0 (39%) litres/week in the TED/TED, PBO/TED, and NT/TED groups, respectively. Thirteen patients





**Figure 1** Step-up approach in the management of short bowel syndrome-intestinal failure. GLP-2: Glucagon-like peptide-2; PPIs: Proton-pump inhibitors.

achieved full enteral autonomy. This trial demonstrated the long-term effectiveness and safety of TED [66].

A further extension of STEPS and STEPS-2 studies is the STEPS-3 study. Long-term treatment with TED in this 1-year, open-label extension trial showed a safety profile consistent with previous studies, with prolonged effectiveness and a further reduction in HPN necessity [67]. A post hoc analysis determined factors associated with the response to TED. Notably, the remaining bowel anatomy, rather than the remaining bowel length, primarily affected the outcome of TED therapy. Patients with jejunostomy or ileostomy (SBS-IF type 1 according to the anatomical classification) experienced the most pronounced benefit from TED compared to patients with colon continuity. The same study outlined how patients with higher baseline PS volume had higher reductions in PS, which means that SBS-IF patients with more severe malabsorption benefit the most from therapy with TED [68].

Safety data from clinical trials of TED reported abdominal distension and gastrointestinal stoma complications as the most frequent adverse events (AEs), and the AE frequency was higher early in the course of treatment and declined thereafter [69]. The capacity of GLP-2 to accelerate the growth of experimental intestinal tumors was known before the introduction of TED [70,71]. A post hoc analysis of STEPS studies found that 50 of 65 patients with remnant colon (77%) underwent a protocol-mandated postexposure colonoscopy. Colon polyps were reported in 12% (9/73) of patients at baseline and 18% (9/50) of patients postexposure. Two patients had polyps at baseline and postexposure. Histology was available for 7 patients: 5 had adenomas (1 serrated, 4 tubular), and none had malignancies or high-grade dysplasia [72].

A large population analysis characterizing 170 patients treated with TED from the United States from 2015 to 2020 found that an overall 5.9% of patients developed posttreatment polyps of the large intestine. Twenty events (12%) of catheter infection were described in the same study within 1 year from the start of administration. Other documented adverse effects were abdominal pain (70 cases, 41.2%), nausea (40 cases, 23.5%), intestinal obstruction (30 cases, 17.6%) and stoma complications (20 cases, 11.8%). Ten patients (6%) developed colon polyps [73].

A French real-life study reported a population of 54 patients with SBS-IF treated with TED. The effectiveness and safety were fully confirmed. Twenty-four weeks after the start of treatment, 85% of patients experienced a reduction in PS of at least 20%, and 24% of patients were weaned off PS [74]. Another real-life cohort of 18 patients treated with TED for a median of 3.2 years was reported. Twelve of these patients achieved a clinical response at 12 mo, which was maintained in most of these patients at 36 mo. Five patients were able to wean off PS, but no predictor was identified due to the small sample [75].

New GLP-2 analogue molecules were studied recently. Apraglutide (TA799-007), which is characterized by high protein binding, resistance to DPP4 cleavage, low clearance and slow absorption after subcutaneous administration, has been highlighted [76]. These features make apraglutide clinically appealing, which suggests the possibility of more delayed dose administration [77].

Apraglutide showed efficacy in studies of animal models of SBS-IF in terms of increases in intestinal length and weight, crypt weight and villous height and lower faecal fat and energy losses [78,79]. The effects on intestinal length and mucosal hypertrophy after discontinuation of TED and apraglutide were also studied in piglets. These two molecules apparently showed similar results in this case: Intestinal growth appeared to be a lasting outcome of treatment with long-acting GLP-2 and persisted for at least 7 d after discontinuation. In contrast, mucosal hypertrophy appeared to regress 7 d after the end of

treatment with both agents[80]. However, these results must be interpreted with caution and need further confirmation. The once weekly administration of apraglutide to neonatal piglets showed superior intestinotrophic effects than a single daily dose of TED and led to increased bowel length and villus height[81].

A recent PBO-controlled, randomized, phase II clinical trial treated eight adults with SBS-IF with once-weekly 5-mg apraglutide or PBO for 4 wk, followed by once-weekly 10-mg apraglutide doses for 4 wk, with a washout period of 6-10 wk between treatments. No severe AEs related to the drug were detected, and comparable safety profiles were observed between the low-dose and high-dose regimens. The main AE detected was an increase in urine output, and the following less frequent AEs were reported in decreasing order: Stoma complications, decreased thirst, oedema, increased weight, and injection site reactions[82]. A phase 3 study in SBS-IF patients treated with apraglutide *vs* PBO is currently ongoing[83].

Glepaglutide is another long-acting analogue of GLP-2 that chemically differs from native GLP-2 by 9 amino acid substitutions and a C-terminal tail consisting of six lysine residues. It has a half-life of approximately 50 h and has been evaluated in a phase II study, where it demonstrated good tolerance and the ability to improve intestinal absorption in SBS patients treated with 1 mg and 10 mg daily glepaglutide[84]. A phase 3 study comparing weekly or twice weekly glepaglutide and PBO administration to SBS patients is currently ongoing[85].

Other molecules are in the preclinical phase of their development. Elsiglutide is a GLP-2 analogue with a long half-life that reduced diarrhoea induced by lapatinib, a tyrosine kinase inhibitor, in a rat model[86]. Dapiglutide is a dual GLP-1 and GLP-2 agonist that showed beneficial effects in a rat model of SBS by improving body weight, promoting intestinal growth, increasing villous height and intestinal length, and reducing watery stool losses[87].

For the duration of therapy with GLP-2 analogues in patients with SBS-IF, the available data indicate that these drugs must be administered over a long life because reversal of the previous need for PS occurs if TED is discontinued[64]. A recent report described 13 patients (one with CD and one with ulcerative colitis) who discontinued TED after a successful clinical outcome. The volume of PS remained stable in the first 4 years but later increased in 12/13 patients up to 9 years after withdrawal[88]. These data support further studies exploring the possibility of the periodic use of GLP-2 analogues for selected SBS-IF patients.

## GLP-2 ANALOGUES IN CROHN'S DISEASE

Knowledge of GLP-2 analogue use in patients with CD is limited. No RCTs specifically address the efficacy and safety of GLP-2 in CD patients with SBS-IF. However, 18 patients with CD were included in the 86 subjects of the STEPS study, 10 in the TED arm and 8 in the PBO arm[65]. Sixteen CD patients were included in the STEPS-2 long-term study[66]. The CD patients in these studies were in the inactive phase of their inflammatory disease, and the concomitant use of immunosuppressants and biologics were exclusion criteria. The subsequent post hoc analysis of the STEPS studies analysing factors associated with the response to TED in patients with SBS-IF found that the effects of TED on PS volume reduction were more pronounced in patients with jejunostomy/ileostomy than in patients with partial colon continuity. Only 10.5% of CD patients had colon in continuity in this study. Therefore, CD patients were likely among the best responders according to this analysis[68].

Subsequent data from real-life studies reported the experiences of TED treatment for CD patients treated with immunosuppressants and biologics and patients with active inflammation. A retrospective cohort study published in 2017 analysed 13 patients with CD and SBS-IF treated with TED for an average of 1 year. Nine of these patients were under parenteral nutrition before beginning TED therapy, and only 1 of them needed parenteral nutrition after TED. All of these patients required intravenous fluids before TED, but only 7 of them required this supplementation after TED. Eight of these patients were treated with biological therapies and/or immunosuppressants. TED was well tolerated in most of these CD patients, with the exception of one patient who intermittently presented with obstructive symptoms that required the cessation of therapy[89].

Two other active CD cases treated with TED were described. The first case was a 38-year-old patient with relapsing perianastomotic disease treated with ustekinumab. This patient received PN daily for SBS and was weaned off after 7 mo of TED. The second patient was 39 years old and had received PN daily since 2003. This patient was treated with vedolizumab and 6-mercaptopurine. After multiple resections, he was left with a jejunocolic anastomosis and 60 cm of residual small bowel length. PN was reduced to 1 night per week after TED[90].

One case of long-term TED use (54 mo) was reported in a patient with multidrug-resistant CD, and beneficial effects on nutritional status, a significant anti-inflammatory effect and reduction in CD clinical activity were observed[91]. A recent real-life cohort of 52 patients successfully treated with TED found that 16 had CD[74]. Another real-life series of 18 patients on TED found that 10 patients had SBS-IF caused by CD, and the 5 who were able to withdraw PS were all CD patients[75]. The findings of these studies are presented in Table 1.

**Table 1 Main studies and case reports on glucagon-like peptide-2 analogues in Crohn's disease with short bowel syndrome**

Ref.	Molecule tested	Number of patients	Number of CD patients	Study type	Main results	Adverse events
Jeppesen <i>et al</i> [64], 2005	Teduglutide	16	12 (in clinical remission)	Pilot open label, phase II	Increased wet weight absorption; decreased urine weight and urine sodium excretion; decreased fecal wet weight and fecal energy content; increased villus height, crypt depth and mitotic index in end-jejunostomy patients	Enlargement of the stoma nipple; mild lower leg oedema; severe AE (dehydration, sepsis, CS) in 4/16, not judged to be related to the drug
Jeppesen <i>et al</i> [65], 2012	Teduglutide	43 (+ 43 PBO)	10 (in clinical remission)	Multicenter, randomized, double blind, PBO-controlled phase III	63% of TED patients had a $\geq 20\%$ reduction of PS volume at week 24 (significant versus 30% of the PBO group); increased serum citrulline (index of intestinal mucosa mass)	Mostly mild GI symptoms (abdominal pain, nausea, stoma complication, or abdominal distension); 7/43 CS; not different from PBO
Schwartz <i>et al</i> [66], 2016	Teduglutide	88	16	2 yr open label extension study	Clinical response ( $\geq 20\%$ reduction of PS volume) in 28/30 (93%) and 66% of PS volume reduction in TED/TED group; 13 reached enteral autonomy	34% abdominal pain; 25% episodes of weight decrease; 39% infections (SAE); 2 CD exacerbations (12% of CD, SAE)
Kochar <i>et al</i> [89], 2017	Teduglutide	13	13 (8 on biologics and/or IS)	Retrospective cohort study (median duration 1 yr)	9 patients on PN at the beginning of therapy; 1 patient still on PN at the end of therapy; PS reduced from median 9000 mL/wk to 3100 mL/wk, 6 patients no PS at the end	Among non-immunosuppressed (5) only 2 minor AE and 1 CS; among immunosuppressed (8) minor AE, 3 CS and 2 pancreatitis
Barberio <i>et al</i> [94], 2019	Teduglutide	1	1 (on EN and adalimumab)	Case report	EN reduction of 50% after 24 wk of TED; EN suspension after 72 wk of treatment	Transient nausea and mild abdominal pain and nausea
Al Draiwesh <i>et al</i> [90], 2019	Teduglutide	2	2 (on biologics)	Case report	Weaning off from PS after 7 mo of TED; improvement in oral intake, reduced stool output, and weight gain; reduction of PN to 1 night/wk	Any reported
Naimi <i>et al</i> [84], 2019	Glepaglutide	16	8	Double-blind randomised phase II trial	1 mg daily glepaglutide reduces the fecal output by 592 mg/d; 10 mg daily glepaglutide reduces the fecal output by 833 mg/d	Stoma complications (73%); injection site reactions (61%); peripheral edema (56%); nausea and abdominal pain (44%); SAEs (stoma obstruction, sepsis) in 4 patients
Joly <i>et al</i> [74], 2020	Teduglutide	54	16	Retrospective multicenter real life cohort	85% of patients were responders (PS reduction $\geq 20\%$ ) at week 24; 24% weaned off PS at week 24	Not specifically collected
Borghini <i>et al</i> [91], 2020	Teduglutide	1	1 (clinically active)	Case report	At least 20% reduction in PS; daily Kcal intake reduction of 15%; reduction in CD activity and severity	Two mild CVC-related infections
Mouillot <i>et al</i> [93], 2020	Teduglutide	1	1	Case report	Reduction of PS and increase of nutrients absorption; hypertrophy of villi at capsule endoscopy; increase in the size of intestinal villi and crypts assessed by biopsy	Not specifically assessed
Puello <i>et al</i> [75], 2021	Teduglutide	18	10	Retrospective single center real life cohort	Response (reduction of $> 20\%$ PS) in: 16 (75%) patients at 12 mo; 10 of 13 (76.9%) patients at 24 mo; 7 of 10 (70%) patients at 36 mo; 3 of 3 (100%) patients at 60 mo; 5 patients (all CD) weaned off PS	Abdominal pain or cramping (3); volume overload (1); taste loss (1); legs edema (2); increase in ostomy size (2)
Eliasson <i>et al</i> [82], 2022	Apraglutide	8	3 (in clinical remission)	Open label phase I-II trial	Weekly 5 mg apraglutide increases urinary output by 714 mL/d; weekly 10 mg apraglutide increases urinary output by 795 mL/d	Polyuria (7/8); any stoma complication (6/8); thirst decrease (4/8) and appetite decrease (3/8); edema (4/8); no SAE related to the drug

CD: Crohn's disease; PN: Parenteral nutrition; PS: Parenteral support; EN: Enteral nutrition; TED: Teduglutide; PBO: Placebo; GI: Gastrointestinal; SAEs: Severe adverse events; CS: Catheter-related sepsis; CVC: Central venous catheter; IS: Immunosuppressives; AE: Adverse events.

Other retrospective and prospective cohorts of SBS-IF patients treated with TED (including a variable proportion of CD patients) were described and recently summarized in a meta-analysis that confirmed the efficacy of TED in adult SBS-IF patients[92]. This analysis suggested a non-significant trend of CD aetiology of SBS-IF as a positive predictor of response and weaning from PS.

A case of intestinal adaptation induced by TED in CD was recently described. The case was a 40-year-old female patient suffering from SBS-IF due to CD since 2001. The patient underwent terminal jejunostomy, with 100 cm of jejunum remaining. SBS and IF resulted, and the woman needed continuous PS. She was recommended to start treatment with TED, and her intestinal status and disease activity were studied at baseline. No active CD was detected, and the intestinal villi appeared normal. After 1 year of continued TED treatment, a new biopsy of intestinal villi was performed and showed an increase of 33% in the length of villi[93].

The efficacy of off-label TED use in a 65-year-old CD patient treated with adalimumab with SBS and enteral nutrition was also described, and the patient was weaned off enteral nutrition after 72 wk[94]. Concerning TED discontinuation, a report described 2 CD patients on chronic TED treatment who were not able to tolerate even a few days withdrawal of the drug[95].

One line of research attempted to determine whether TED had anti-inflammatory activity in CD based on the results of the use of glucagon-like peptides in animal models of colitis[96]. An RCT was performed on 100 CD patients with moderately to severely active disease who were treated with TED (0.05, 0.10, or 0.20 mg/kg) daily for 8 wk or PBO. Seventy-one patients completed the study, and the results showed numerically higher response and remission rates in all treatment groups compared to PBO, but these differences were not statistically significant. The results were more substantial in the group treated with the higher dose (44% response and 32% remission *vs* 32% response and 20% remission in the PBO group). It is questionable whether the clinical disease activity indices modifications described in this study were mostly due to the effect of TED on diarrhoea because no significant modification of C-reactive protein was detected. AEs were not different between the PBO and treatment groups[97]. This last result is particularly relevant, because it came from a controlled study on a relevant number of patients with active CD, although not affected by SBS-IF. The good safety profile in this setting justifies the use of GLP-2 analogues in patients with SBS-IF and active CD, but more data on this specific population are needed. Data on the use of the new GLP-2 analogues (apraglutide and glepaglutide) in CD are lacking.

## CONCLUSION

SBS-IF is a rare condition that affects patients who undergo several intestinal resections due to CD and other gastrointestinal conditions. Although surgery rates in CD have declined in recent decades due to improved diagnostic and pharmacological modalities, the rate of CD patients developing SBS-IF (albeit low) has not been reduced. Several mechanisms are adopted by organisms to adapt to intestinal functional reduction. However, these adaptations are often not sufficient to avoid the clinical impact and long-term complications of SBS-IF, and several patients require HPN. The main therapeutic approaches consist of PS and symptomatic therapy. Yet, PS is associated with several AEs that complicate patient management, such as catheter-related complications, liver and metabolic disease, iron deficiency anaemia, and manganese toxicity.

New molecules and therapeutic approaches have been studied in recent years. The GLP-2 analogue TED demonstrated a relevant clinical utility for SBS-IF patients, and it significantly reduced HPN volume and/or days of infusion, allowing enteral autonomy in some patients. However, because this therapy is likely life-long or of long duration, more data are needed on the long-term safety and cost-effectiveness. Recent further consideration has been given to new GLP-2 analogues that have undergone phase I and II studies, including apraglutide and glepaglutide. These agents showed low clearance and slow absorption after subcutaneous administration, which allowed for a single weekly administration. Relatively scant data are available on the use of GLP-2 analogues in CD patients with SBS-IF. However, signals from RCTs and real-life observations indicate that TED is efficacious and well tolerated by CD patients, even if they are being treated with immunosuppressants and/or biological agents. More data are needed on the use of GLP-2 analogues in patients with active CD to clarify their safety and efficacy in this setting. This new pharmacological approach may improve the quality of life of patients with CD and SBS-IF and reduce their dependence on artificial nutrition. Clinical studies specifically addressing this peculiar population are warranted.

## FOOTNOTES

**Author contributions:** All authors contributed to the conception and design of the study, drafting the article or making critical revisions related to important intellectual content of the manuscript; Pizzoferrato M, Cammarota G and Guidi L involved in the final approval of the version of the article to be published.



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