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REVIEW

Use of teduglutide in adults with short bowel syndrome–associated intestinal failure

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Abstract

Short bowel syndrome (SBS) is a rare gastrointestinal disorder associated with intestinal failure (SBS-IF) and poor health-related outcomes. Patients with SBS-IF are unable to absorb sufficient nutrients or fluids to maintain significantly metabolic homeostasis via oral or enteral intake alone and require long-term intravenous supplementation (IVS), consisting of partial or total parenteral nutrition, fluids, electrolytes, or a combination of these. The goal of medical and surgical treatment for patients with SBS-IF is to maximize intestinal remnant absorptive capacity so that the need for IVS support may eventually be reduced or eliminated. Daily subcutaneous administration of the glucagon-like peptide 2 analog, teduglutide, has been shown to be clinically effective in reducing IVS dependence and potentially improving the health-related quality of life of patients with SBS-IF. The management of patients with SBS-IF is complex and requires close monitoring. This narrative review discusses the use of teduglutide for patients with SBS-IF in clinical practice. The screening of patient eligibility for teduglutide treatment, initiation, monitoring of efficacy and safety of treatment, adapting or weaning off IVS, and the healthcare setting needed for SBS-IF management are described, taking into consideration data from clinical trials, observational studies, and clinical experience.

KEYWORDS
adults, intestinal failure, intestinal transplantation, intravenous supplementation, parenteral nutrition, short bowel syndrome, teduglutide

INTRODUCTION

Teduglutide is a glucagon-like peptide-2 (GLP-2) analog that has been approved for the treatment of patients ≥1 year of age with short bowel syndrome (SBS) who are dependent on parenteral support.[1,2] SBS is a rare malabsorptive condition of the gastrointestinal (GI) tract, characterized by diarrhea or high ostomy output, malnutrition, and dehydration, that can result in SBS-associated intestinal failure (SBS-IF) requiring intravenous supplementation (IVS) of macronutrients and fluids and electrolytes (FEs) to maintain nutrition status. SBS-IF often occurs as a result of extensive intestinal resection (typically resulting in a bowel length ≤200 cm in adults), commonly due to inflammatory or vascular disease, trauma, surgical complications, or congenital abnormalities.[3–7] SBS-IF can also be present in patients with a bowel length >200 cm if there is additional impairment of remnant bowel function (functional SBS-IF).[7] There are three anatomical subtypes of SBS, classified by the remnant bowel in place: SBS with an end small intestine ostomy (jejunostomy or ileostomy) (SBS-J or anatomic type 1 SBS), SBS with jejunocolic anastomosis (SBS-JC or anatomic type 2 SBS), and SBS with jejunoileal anastomosis with an intact colon and the presence of the ileocecal valve (SBS-JIC or anatomic type 3 SBS) (Figure 1).[8,9] From the time of diagnosis, 10-year survival rates for adults with SBS-IF are approximately 50%–60%, with overall outcomes in terms of reversibility and mortality depending on a variety of factors, such as underlying disease, anatomy, extent of dependence on IVS, complications, comorbidities, and patient age.[10–12]

Patients with SBS-IF require IVS consisting of partial or total parenteral nutrition (PN), intravenous FEs, or a combination of these.[3] IVS may be administered either in the hospital (for acute or prolonged acute intestinal failure [IF]) or outside a hospital setting (for chronic IF), the latter being termed home PN (HPN) (Table 1).[6,7] Complications may arise from both SBS-IF itself and the life-sustaining IVS support, with the direct cause being difficult to separate in some instances, such as IF-associated liver disease, chronic renal failure, and metabolic bone disease (eg, osteopenia and osteoporosis). Complications related mostly to SBS-IF include dehydration, magnesium deficiency, electrolyte and acid-base

TABLE 1 ESPEN guidelines on the functional classification of IF.

IF type	Description
I	Acute, short term, and often self-limiting
II	Prolonged acute condition
	Often in metabolically unstable patients
	Requires multidisciplinary care and IVS over weeks/months
III	Chronic condition
	In metabolically stable patients
	Requires IVS over months/years
	Reversible or irreversible

Note: Adapted from Pironi et al.[6]

Abbreviations: ESPEN, European Society for Clinical Nutrition and Metabolism; IF, intestinal failure; IVS, intravenous supplementation.

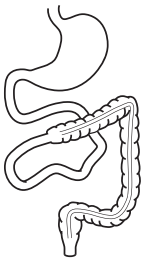
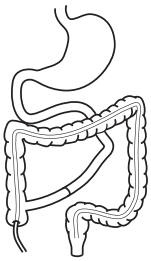
	Jejunostomy or ileostomy (SBS-J)	Jejunocolic anastomosis (SBS-JC)	Jejunoileal anastomosis (SBS-JIC)
			
Description	Ileum, colon, and part of jejunum are resected; stoma created in abdomen	Ileum, portion of jejunum, and portion of colon are resected and remaining sections joined	Parts of jejunum and ileum are resected and the remnant parts of the small bowel are anastomosed; ileocecal valve and entire colon are present
Probability of IVS dependence	Variable[a] but higher in patients with <115 cm jejunum remaining[b]	Variable[a] but generally higher in patients with <60–65 cm jejunum remaining[b]	Low, but increased in patients with <35 cm small bowel remaining[b]

FIGURE 1 Anatomical classification of SBS-associated intestinal failure. [a]Depending on the length of the remnant jejunum. [b]Measured from the ligament of Treitz. IVS, intravenous supplementation; SBS, short bowel syndrome.

alterations, biliary and renal stones/injury, and some metabolic complications (eg, D-lactic acidosis),[8] whereas complications due to IVS include catheter-related bloodstream infection (CRBSI) or catheter-related malfunction and venous thrombosis.[8]

The volume and type of IVS are independently associated with patient outcomes and major IF/HPN complications and are, therefore, indicators of the severity of chronic SBS-IF.[8,13] Patients with chronic SBS-IF who require only intravenous FEs have less severe SBS-IF than those receiving PN support. In addition, for patients requiring low-volume PN (<1 L/day), the odds of weaning off IVS support are significantly increased, and the odds of death and major complications, such as CRBSI and IF-associated liver disease, are significantly decreased compared with individuals needing higher-volume PN support.[13] In the 1–3 years following resection, spontaneous intestinal adaptation occurs and results in the intestine becoming more efficient at absorbing nutrients and fluids, contributing to a reduction in IVS dependence or even weaning.[13] Intestinal adaptation involves the elongation, thickening, and dilatation of the intestinal remnant, with increases in small bowel villus height and diameter, crypt depth, and epithelial cell proliferation.[14] Furthermore, in SBS with a colon in continuity, a delay in gastric emptying and intestinal transit time may develop.[14,15] Spontaneous intestinal adaptation is a highly variable process, unique to each patient, and is influenced by the remnant GI tract length and anatomy as well as by the quality and quantity of oral/enteral nutrition.[14,15] In general, intestinal adaptation is more pronounced in the ileum and colon than in the jejunum.[9,14]

Intestinal rehabilitation is the ultimate goal of treatment, maximizing the intestinal remnant absorptive capacity so that the need for IVS is eventually reduced or eliminated, thereby alleviating the daily burden of this debilitating condition.[16] Improving health-related quality of life (HRQoL) is a treatment goal potentially related to IVS because a negative association between the number of IVS infusions per week and HRQoL has been observed using validated patient-reported outcome questionnaires, such as the HPN-Quality of Life questionnaire[17] and the PN Impact Questionnaire.[18]

To achieve the treatment goals, a multidisciplinary team of healthcare professionals (HCPs) is required to educate and closely monitor patients with SBS-IF.[6,8] Patient education should include helping patients to develop a general understanding of the disease, the provision of guidance on HPN management, and dietary counselling (including hydration, macronutrients, and micronutrients).[8,19,20] Management of SBS-IF also includes the use of antidiarrheal/antimotility agents, antisecretory agents, bile salt binders (in patients with colon in continuity), antibiotics for small intestinal bacterial overgrowth, and oral rehydration solution.[12,20,21] Surgical options include reconstruction (to preserve and maximize the function of the intestinal remnant, to augment intestinal length, mostly in pediatric patients, or both) or intestinal transplantation.[12] More recently, teduglutide, a recombinant analog of GLP-2, has been added to the treatment regimen of selected patients with SBS-IF.[6] Current therapeutic approaches for adults with SBS-IF are described in Table 2.

TABLE 2 Current therapeutic approaches for adults with short bowel syndrome–associated intestinal failure.

Therapeutic approach	Example
Nutrition and hydration support	Fluid and electrolyte management
	Macronutrients and dietary therapy
	Micronutrients and trace element supplementation
Medical management of GI symptoms	Antisecretory agents
	Antimotility/antidiarrheal drugs
	Antibiotics
	Bile salt binders
Surgical options	Nontransplant or GI reconstructive surgery
	Intestinal transplantation
Growth factor therapies[a]	GLP-2 analog (teduglutide)

Abbreviations: GI, gastrointestinal; GLP-2, glucagon-like peptide-2.
[a]Human growth hormone is also approved by the US Food and Drug Administration for the treatment of adults with short bowel syndrome.

Teduglutide—a recombinant analog of GLP-2

GLP-2 is a trophic hormone secreted by intestinal L cells of the lower small and large intestinal mucosa in response to the presence of nutrients in the gut lumen.[22] GLP-2 enhances intestinal capacity to absorb nutrients by promoting intestinal crypt cell proliferation, inhibiting enterocyte apoptosis and gastric acid secretion, decreasing small intestinal motility, and increasing mesenteric blood flow.[22,23] In murine models of SBS, teduglutide partially restored small intestinal epithelial function through an altered distribution of claudin-10, which facilitates sodium recirculation for sodium-coupled glucose transport and water absorption, thereby contributing to improved nutrition and hydration status.[24]

Endogenous GLP-2 has a mean elimination half-life of 7 min, whereas teduglutide, which has a single amino acid substitution, resists degradation and has a mean elimination half-life of ~2 h in healthy individuals and 1.3 h in patients with SBS-IF.[1,2] Teduglutide is approved in the United States, Europe, and Japan for use in adults and children (≥1 year old) with SBS-IF who are IVS dependent. The European Society for Clinical Nutrition and Metabolism (ESPEN) and national guidelines suggest that teduglutide should be the first choice for patients with SBS-IF who have been carefully selected as candidates for growth factor treatment.[6,25] In phase 3 clinical studies, teduglutide enhanced intestinal absorption and significantly reduced IVS requirements in 63%–67% of patients with SBS-IF.[26–29]

The clinical safety and efficacy of subcutaneous teduglutide 0.05 mg/kg/day in adult patients were demonstrated in the Study of Teduglutide Effectiveness in PN-dependent SBS Subjects (STEPS) randomized, placebo-controlled clinical trial (ClinicalTrials.gov identifier: NCT00798967)[30] and its open-label extensions (STEPS-2 [NCT00930644][31] and STEPS-3 [NCT01560403][16]). Overall, in the STEPS trials, the greatest reductions in IVS volume were observed in individuals with the longest exposures to teduglutide. Long-term treatment (up to 3.5 years) with teduglutide in patients with SBS-IF was associated with further reductions in IVS requirements and an increased likelihood of achieving independence from IVS.[16,30,31]

In the STEPS trials, the most frequently reported adverse events (AEs) were GI in origin, consistent with patients having a diagnosis of SBS-IF and the intestinotrophic actions of teduglutide. Abdominal pain was the most common AE with teduglutide treatment. Other frequently reported AEs were CRBSI, headache, nausea, nasopharyngitis, vomiting, and decreased weight. The most common serious AEs included catheter-related complications (including CRBSI), small intestinal obstruction, and fever.[16,30,31] Owing to its mechanism of action as a trophic hormone analog and consistent with preclinical study findings, teduglutide has the potential to cause hyperplastic changes in the GI and hepatobiliary tracts. In STEPS-2, GI polyps were reported in 9 of 51 patients who underwent colonoscopies within or at the end of the 24-month treatment period with teduglutide; there were no cases of intestinal dysplasia or malignancy.[31] To date, no carcinogenic effect has been observed in teduglutide's clinical use.[2,32]

As with all clinical trials, patients who met strict criteria were enrolled in the STEPS trials, so such observations from clinical trials may not be generalizable. However, real-world data have studied teduglutide in patients consistent with these criteria.[33–39] Data from observational studies demonstrate the safety, tolerability, and clinical utility of teduglutide in the treatment of adults with SBS-IF in line with the results of clinical trials.[33–39] Compared with clinical trials, which often have narrow inclusion criteria, observational studies allow for the treatment of a wider demographic of patients.[40] In a French cohort of individuals with SBS-IF who received teduglutide for 6 months, 85% ($n = 46/54$) of patients responded to teduglutide treatment with a reduction in IVS volume of at least 20% and a mean reduction in IVS-dependent days of 1.5 days per week, and 24% ($n = 13/54$) of patients achieved IVS independence.[39] Similar results were achieved in a German cohort study,[34] in which IVS independence was achieved by 21% ($n = 4/19$) of patients. A clinically significant reduction of IVS volume (defined as ≥20% reduction in IVS volume) was observed in 79% ($n = 15/19$) of patients with onset between 1 and 45 weeks. Furthermore, significant IVS reductions were observed, ranging from ~20% in patients treated for 3 months to 45% in patients treated for 2 years. This was accompanied by an increase in IVS-free days.[34] A separate German cohort study of 44 patients found that absolute IVS volume significantly decreased after 6 and 12 months of teduglutide treatment. Furthermore, 68% ($n = 30/44$) achieved a ≥20% reduction in IVS volume after 12 months and 14% ($n = 6/44$) of patients achieved IVS independence.[41]

The time of response to teduglutide treatment is highly variable, most likely owing to the heterogeneity of the SBS population. However, it is difficult to predict the time to response to teduglutide; the drug's effectiveness can be detected within the first weeks of treatment in some patients, whereas for others it may take up to 12 months.[33,34,36,39]

Safety data from observational studies are consistent with those reported from the randomized controlled trials and their long-term extension studies.[33,34,36,39] Data from the ongoing, prospective, observational, multinational SBS registry demonstrate that teduglutide has clinical benefits in a real-world setting for up to 4 years of treatment; no new safety signals were identified, and serious AEs were consistent with those from previously reported safety data.[42–44]

Post hoc analyses of STEPS and STEPS-2 data identified predictors of teduglutide response. Subgroup analyses suggest that the presence of stoma, absence of colon in continuity, or an etiology of inflammatory bowel disease (IBD) may be positively associated with an early response, whereas being female, having vascular disease as the cause of major intestinal resection, and ileocecal valve presence were negatively associated with an early response.[45] Patients with the highest IVS volume requirements at baseline had the greatest reduction in

volume at week 24, and among those with the largest reduction (≥1500 ml/day), most had a jejunostomy or ileostomy and IBD was the most common cause of their SBS-IF.[46] Indeed, patients who were more likely to experience a response to teduglutide within 24 weeks had an absence of the distal/terminal ileum or ileocecal valve, a lower likelihood of having colon in continuity, and a lower percentage of colon remaining. The majority of patients who did not respond to teduglutide within 24 weeks eventually responded during the extension phase (STEPS-2); the characteristics identified are therefore indicative of an early response rather than an absolute response, which may inform more accurate treatment expectations and encourage persistence with treatment.[47] Furthermore, a systematic review and meta-analysis of the published literature (which included 10 studies) found that the presence of colon in continuity reduced the response rate (defined as ≥20% reduction in IVS volume with respect to baseline) but increased the rate of weaning off IVS, and an etiology of Crohn's disease was found to be a nonsignificant predictor of increased response and weaning rates.[48]

IDENTIFICATION OF PATIENTS ELIGIBLE FOR TEDUGLUTIDE TREATMENT

Clinical trials show that treatment with teduglutide should not be initiated until it can reasonably be assumed that a patient is stable after a period of postsurgery intestinal adaptation, which is usually the case 12 months after the last intestinal resection, but may range from 6 months to >36 months.[2,49] IVS should be optimized and stabilized before the start of treatment.[34,50]

To assess eligibility for teduglutide treatment, HCPs need to review the patient's medical history and assess a number of factors, such as individual needs (including psychosocial traits, lifestyle, and goals), current clinical status, nutrition status, and possible nutrient deficiencies.[39,50] Patients who are potentially eligible for teduglutide treatment may require further assessments to determine their suitability; a checklist of clinical evaluations to assess eligibility is provided in Table 3 and summarized below.[51,52]

GI anatomy

The length, structure, health, and function of the remnant bowel should be assessed to determine the anatomical type of SBS and to investigate for the presence of strictures, blind loops, unclear anastomotic sites, and the activity of the underlying disease, such as inflammation in the case of IBD or mucosal damage in the case of ischemic vascular disease.[1,2] Colonoscopy, gastroscopy, radiological imaging, and abdominal ultrasound are the diagnostic procedures to be used, adapted to each individual patient's specific requirements. ESPEN guidelines indicate that restoration of the GI tract's continuity should be considered for each case[6] and that intestinotrophic treatment should be given only if a reconstructive procedure is not feasible or has already been conducted.[6,25]

Laboratory assessment

Renal function should be tested by assessing levels of blood urea nitrogen, serum creatinine, and the estimated glomerular filtration rate. In addition to measuring body weight, height, and body mass index, considerations should be given to assess body composition by bioimpedance analysis. Complete blood count, electrolytes (serum and urinary Na^+, K^+, Cl^-, Ca^{2+}, Mg^{2+}, and PO_4^{3-}), vitamins, and trace elements should be measured and monitored as clinically indicated and recommended by guidelines in the individual patients.[34] Relevant parameters to assess fluid and sodium balance are 24-h urinary volume and urinary sodium concentration. Acid-base status should be assessed by monitoring serum chloride and bicarbonate concentrations to survey for acidotic or alkalotic imbalances; any imbalance should be addressed by medical treatment and IVS adaptation accordingly. Other laboratory values to determine eligibility include liver tests (levels of plasma alanine transaminase, aspartate transaminase, alkaline phosphatase, gamma-glutamyl transpeptidase, total and conjugated bilirubin, total protein, serum albumin level, and the prothrombin time international normalized ratio) and plasma lipase level. Baseline laboratory assessments should be performed within 6 months prior to initiating treatment with teduglutide.

Contraindications—does the patient meet the criteria for teduglutide?

All contraindications, warnings, and precautions from the summary of product characteristics document for teduglutide must be considered before the initiation of therapy.[1,2,52] Teduglutide is contraindicated in patients with active malignancy and those with a history of malignancy in the GI tract, hepatobiliary tract, or both, including the pancreas, within the past 5 years.[1,2,32,51,53] Patients with signs and symptoms of small bowel obstruction should be

TABLE 3 Checklist of clinical assessments performed to assess eligibility for teduglutide treatment.

Stage	Checklist of clinical assessments to assess eligibility
Define patient's individual SBS-IF status	◦ SBS type (anatomy and length of the remnant bowel) ◦ Duration of postsurgery intestinal adaptation (months or years) ◦ Oral feeding ◦ Type and volume of IVS (including severity classification of CIF, according to ESPEN[a]) ◦ Patient's experiences or manifest complications of SBS-IF: CRBSI, catheter dysfunction or thrombosis, IFALD, gallbladder stones, kidney stones, or osteopenia ◦ IVS program stability ◦ Hydration status (including fluid and electrolyte balance) ◦ Nutrition status
Screening for patient history	◦ Underlying disease, comorbidities, GI strictures, history of GI obstruction, history of cancer, severe heart failure with episodes of congestive decompensation in particular, chronic kidney disease, hepatobiliary and pancreatic disease, or allergies
Patient adherence to treatment	◦ Check for willingness of patient to participate in treatment, stabilization period of IVS, and ability to self-administer/have a carer administer HPN
Initial clinical assessments[b]	◦ Presence of polyps and GI anatomy assessment: colonoscopy, gastroscopy, and abdominal ultrasound ◦ Assessment of underlying GI disease (eg, IBD) ◦ Liver function tests: levels of plasma alanine transaminase, aspartate transaminase, alkaline phosphatase, gamma-glutamyl transpeptidase, and total and conjugated bilirubin; prothrombin time INR; and plasma concentrations of total protein and serum albumin ◦ Pancreas test: plasma lipase levels ◦ Renal function test: levels of blood urea nitrogen and serum creatinine, glomerular filtration rate, and urine analysis ◦ Cardiovascular function assessment: blood pressure, heart rate, and electrocardiogram; evaluate the need for cardiologic consultation ◦ Biological parameters: blood counts, C-reactive protein level

Abbreviations: CIF, chronic intestinal failure; CRBSI, catheter-related bloodstream infection; ESPEN, European Society for Clinical Nutrition and Metabolism; GI, gastrointestinal; HPN, home parenteral nutrition; IBD, inflammatory bowel disease; IF, intestinal failure; IFALD, intestinal failure–associated liver disease; INR, international normalized ratio; IVS, intravenous supplementation; PN, parenteral nutrition; SBS, short bowel syndrome; SBS-IF, short bowel syndrome–associated intestinal failure.

[a]Severity classification of CIF[13]: CIF requiring IVS with fluids and electrolytes alone is less severe than CIF requiring IVS of PN admixtures; the severity of CIF requiring IVS of PN progressively increases in parallel with the increase of the volume of the PN admixture, calculated on a weekly basis as the daily mean of the total volume infused per week (volume per day of infusion × number of infusions per week/7 [ml/day]): PN1 ≤1000, PN2=1001–2000, PN3=2001–3000, and PN4 >3000.

[b]Perform tests with the patient's consent to define their eligibility for teduglutide treatment further.

evaluated prior to initiating treatment with teduglutide.[1] Colonoscopy, abdominal ultrasound, and gastroscopy are performed on all patients before the initiation of teduglutide treatment to assess for the presence of polyps and to exclude neoplastic disease as well as to clarify unclear anatomic situations or disease activity in the GI remnant (eg, Crohn's disease). In some of these situations, further imaging studies may be required, such as small bowel follow-through or computed tomography/magnetic resonance enterography. A post hoc analysis of data from the STEPS study series, investigating colon polyps before and after teduglutide treatment, reported a polyp detection rate of 12% in patients with SBS-IF who were aged 39–75 years. Although this rate falls in the lower range of the detection rate in the general patient population with SBS-IF, it supported the recommendation for polyp screening via colonoscopies before and during treatment, as the identification of any cancers at baseline would preclude patients from initiating teduglutide therapy. Furthermore, it would allow for the detection and removal of polyps that may be at risk of progression following the initiation of teduglutide treatment.[54] Despite this recommendation, a retrospective analysis of a large population-based commercial database found that, between 2015 and 2019, 170 adult patients with SBS-IF were prescribed teduglutide, of whom 47% did not have a colonoscopy prior to initiating therapy.[55] As recent

care reports showed the de novo development of upper GI adenomas in patients receiving teduglutide, gastroscopy before and during teduglutide treatment is advised.[56,57]

Individual needs and patient education

Suitable candidates for teduglutide treatment should be willing to comply with the requirements of therapy, including daily self-administered subcutaneous injections and regular monitoring by HCPs. Preplanning and shared decision making between HCPs and the patient (as well as their caregivers/families) before initiating teduglutide treatment allows for a well-coordinated treatment plan with realistic treatment goals.[50] According to ESPEN guidelines, patients should be informed of the potential benefits and risks associated with teduglutide treatment.[6] Topics for discussion should include managing expectations around the reduced need for, or weaning off, IVS (eg, benefits/risks of weaning strategies based on frequency vs daily volume), adaptation of the oral diet (eg, hyperphagia or a hypercaloric diet), and HRQoL improvement. Information about potential AEs and risks of treatment (eg, no response to treatment or transient volume imbalances) and the need for regular monitoring (eg, fluid balance and endoscopic screening procedures for potential development of polyps or preneoplastic conditions) should also be provided. In accordance with ESPEN guidelines, patients should receive ongoing dietary counselling guided by an expert dietitian and be made aware of the possibility of the need for lifelong teduglutide therapy.[6] For patients with a stoma, information about possible stoma nipple size enlargement, with guidance on how to adjust and enlarge the hole in the stoma pad, as well as adequate training on the injection technique for subcutaneous administration of teduglutide, should be provided.

Cost effectiveness

Teduglutide is a costly treatment, with an estimated annual cost of $300,000 per patient in the US.[58] Although the safety and efficacy of teduglutide treatment have been extensively reported, studies evaluating the cost effectiveness of teduglutide treatment are minimal. A study of published direct medical costs concluded that teduglutide is not cost effective in adult patients with SBS-IF when compared with no treatment, but acknowledge that subpopulations that demonstrate maximum benefit could be cost saving.[59] ESPEN guidelines acknowledge that specialists in IF should consider the benefit and clinical meaningfulness of treatments vs that of the inconveniences, adverse effects, potential risks, and cost effectiveness.[60]

INITIATION AND ONGOING MONITORING OF PATIENTS TREATED WITH TEDUGLUTIDE

Clinical parameters assessed for safety and efficacy at teduglutide initiation and teduglutide treatment are listed in Table 4.

Following the selection and education of eligible patients, teduglutide treatment may be started. Subcutaneous administration of 0.05 mg/kg teduglutide is the recommended daily dose. Typically, the starting dose of teduglutide (0.05 mg/kg/day) is maintained throughout treatment; however, owing to the heterogeneity of the SBS population, a carefully monitored down-titration of the daily dose may be considered for individuals who have difficulty coping with adverse reactions, to optimize tolerability to the drug. For patients with moderate to severe renal impairment, the teduglutide dose should be reduced by half.[1,2,34,61]

Very close monitoring of the safety and effectiveness of teduglutide in patients with SBS-IF, especially during the initial weeks of treatment, should take place to be able to quickly adapt IVS volume, content, or timing or to discontinue teduglutide therapy (Figure 2).[1,2]

Clinical parameters that need to be monitored at the start of teduglutide treatment are the same for patients with all anatomical subtypes of SBS. However, owing to accelerated gastric emptying, gastric hypersecretion, and poor adaptation following resection, individuals with SBS-J are more susceptible to rapid changes in fluid balance and hydration status and should be monitored more closely than those with other types of SBS; this may even be more evident during teduglutide-induced changes or AEs. The maintenance of FE balance is the mainstay of monitoring, together with renal function and body weight.[46] The presence of edema as well as a day-by-day weight gain may indicate insufficient reductions in IVS following the initiation of teduglutide treatment.[32] In teduglutide studies, edema and fluid retention were most common in patients with the highest parenteral support requirements at baseline; these patients showed the fastest and greatest reductions in parenteral support requirements with teduglutide.[32] The presence or development of hyperphagia was previously identified as an independent predictor for reduction and weaning off IVS from observational studies.[39] Moreover, as nausea is common during the first weeks of teduglutide treatment, close monitoring of oral intake is recommended following the initiation of therapy to ensure nutrition needs are met.[39]

TABLE 4 Checklist of clinical assessments and monitoring performed at teduglutide initiation and during treatment.

Stage	Checklist of clinical assessments and monitoring
At initiation of teduglutide treatment	◦ Body weight, BMI, and BIA (nutrition and hydration status) ◦ Oral food intake ◦ 24-h (patients receiving daily IVS) or 48-h (on consecutive day on and day off IVS, in patients not receiving daily IVS) fluid balance: IVS volume, oral fluid intake, urinary output assessment, and intestinal stoma output or stool assessment (number, weight, frequency, and consistency) – In patients receiving IVS <7 days per week, the 48-h assessment should include two consecutive days on and days off IVS ◦ Serum and urinary sodium (concentration and 24- or 48-h excretion) ◦ Other serum and urinary electrolyte levels (Cl^-, K^+, Mg^{2+}, Ca^{2+}, PO_4^{3-}) and serum bicarbonates, as required according to individual patient clinical features ◦ Liver function tests: levels of plasma alanine transaminase, aspartate transaminase, alkaline phosphatase, gamma-glutamyl transpeptidase, and total and conjugated bilirubin; prothrombin time INR; and plasma concentrations of total protein and serum albumin ◦ Pancreas test: plasma lipase ◦ Renal function test: levels of blood urea nitrogen and serum creatinine, glomerular filtration rate, urine analysis ◦ Biological parameters: blood counts, C-reactive protein level ◦ Plasma citrulline level ◦ Beta-human chorionic gonadotropin level[a]
During treatment with teduglutide (perform safety and effectiveness monitoring every few weeks at the beginning of treatment, followed by regular monitoring [see Figure 2])	◦ Vital signs, body weight, BMI, and BIA (nutrition and hydration status) ◦ Oral food intake ◦ 48-h fluid balance: IVS volume, oral fluid intake, urinary output assessment, and intestinal stoma output or stool assessment (number, weight, frequency, and consistency) ◦ Serum and urinary sodium (concentration and 48-h excretion) ◦ Presence of edema and vital signs (fluid overload) ◦ Other serum and urinary electrolyte levels (Cl^-, K^+, Mg^{2+}, Ca^{2+}, PO_4^{3-}) and serum bicarbonates ◦ Liver function tests: levels of plasma alanine transaminase, aspartate transaminase, alkaline phosphatase, gamma-glutamyl transpeptidase, and total and conjugated bilirubin; prothrombin time INR; and plasma concentrations of total protein and serum albumin ◦ Pancreas test: increase in plasma lipase levels may occur (however, clinical relevance is unclear currently) ◦ Renal function test: levels of blood urea nitrogen and serum creatinine, glomerular filtration rate, and urine analysis ◦ Biological parameters: blood counts and C-reactive protein level ◦ Plasma citrulline level ◦ Adverse event screening (common and serious) ◦ Required adaptation of concomitant medications ◦ Presence of polyps and GI anatomy assessment: colonoscopy, gastroscopy, and abdominal ultrasound (after 1 year of treatment and then repeated every 3–5 years) ◦ Assessment for any underlying GI disease (eg, IBD)

Abbreviations: BIA, bioelectrical impendence analysis; BMI, body mass index; GI, gastrointestinal; IBD, inflammatory bowel disease; INR, international normalized ratio; IVS, intravenous supplementation.

[a]Test for pregnancy; avoid the use of teduglutide during pregnancy.

Following treatment initiation, patients should be closely monitored for teduglutide-related changes; these may include signs and symptoms of fluid overload (eg, rapid weight gain and urine output changes and novel or aggravated edema), which can occur occasionally even within the first 4 weeks of treatment.[52] In addition to maintenance or adjustments to IVS volume, reduction in energy requirements can also occur. Reduction in IVS energy requirements can be determined by estimating energy balance, principally by using measures of changes in food intake, fluid balance, and body weight. Such measures include measured or calculated calorie requirements per kg of body weight and oral intake by 24-h patient dietary recall (or diary), effective intestinal

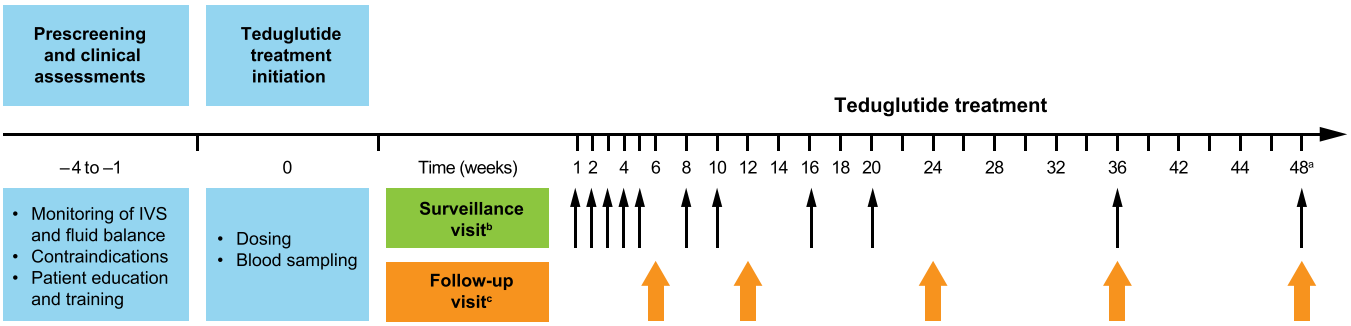


FIGURE 2 Monitoring regimen for teduglutide treatment. [a]After 48 weeks patients are monitored biannually for as long as teduglutide treatment is ongoing. [b]Surveillance visit with specialist nurse: monitoring of adverse events and fluid balance; the black arrows indicate blood sampling. [c]Follow-up visit with physician, specialist nurse, and dietitian: assessment of teduglutide effectiveness and side effects, monitoring of adverse events and IVS, adjustments to IVS (if required), blood sampling, and assessment of nutrition and hydration status (broad orange arrows). IVS, intravenous supplementation.

TABLE 5 IVS volume adjustment based on 48-h urine output used in STEPS.

48-h urine output[a]	IVS action
<1.0 L/day or target based on stabilized urine output	Increase IVS by ≥10% (week 2) or to previous level
≥1.0 L/day but <baseline	If the patient is dehydrated or inadequately nourished, increase IVS. If not dehydrated, maintain IVS
0% to <10% increase over baseline	Maintain IVS
≥10% increase over baseline	Reduce IVS by ≥10% of stabilized baseline level up to a clinically appropriate amount (maximum of 30%)

Note: Adapted from Jeppesen et al.[30]

Abbreviations: IVS, intravenous supplementation; STEPS, Study of Teduglutide Effectiveness in Parenteral Nutrition–dependent Short Bowel Syndrome Subjects.

[a]Baseline urine output is the volume obtained during the stabilization period before treatment is initiated; in patients receiving IVS <7 days per week, the 48-h assessment should include two consecutive days on and off IVS.

absorption, energy intake by IVS, and body weight and composition variations.[6,62,63] An algorithm developed in STEPS for IVS adjustment based on 48-h urine output can be used in clinical practice for guidance on reducing IVS (Table 5).[30] This algorithm is particularly important for patients with SBS-J who are highly dependent on fluids. For patients with SBS-JC, monitoring may be more focused on energy balance (determined by weight, general health status, and frequency and consistency of stools). Following an observed reduction in IVS volume, energy requirements, or both, additional monitoring should be performed after 2 weeks.

The frequency of monitoring may be adapted based on an individual's AEs, and assessments should be performed consistently by the expert treating physician.[64] Results of a post hoc analysis pooling safety data from four clinical trials (including the STEPS trials) showed that most treatment-related GI AEs were reported in the first 12 or 24 weeks after the initiation of teduglutide treatment and appeared to resolve with continued treatment.[32]

The enhancement of fluid absorption during teduglutide treatment can potentially lead to fluid overload, which, although classified as an AE, may indicate a response to teduglutide.[32] The patient should be advised about the importance of monitoring by recording fluid balance (oral intake, urine output, and stoma characteristics) as well as asked to communicate with HCPs regarding unexpected changes or any concerning symptoms (such as loss of appetite, vomiting, and intestinal pain, which might indicate intestinal obstruction).[50]

Gallbladder, biliary tract, and pancreatic diseases have been previously reported; therefore, it is recommended that laboratory tests for liver abnormalities, as performed at the start of treatment, are repeated every 6 months or more frequently at the physician's discretion. If clinically meaningful changes are observed, further clinical evaluations of the gallbladder, biliary tract, or pancreas are recommended. Patients receiving oral concomitant medicinal products that require titration, such as warfarin, or have a narrow therapeutic

index (eg, cardiovascular drugs, immunosuppressants, opioids, or psychotropic medications) should be monitored closely because of the potential for increased absorption while receiving teduglutide.[1,2]

A surveillance colonoscopy to identify colon polyps should be conducted after 1 year of teduglutide treatment; subsequent colonoscopies (or an alternative imaging method, such as computed tomography colonography) should then be repeated at least every 3–5 years while the patient is receiving teduglutide treatment. If polyps are neoplastic, teduglutide must be discontinued and appropriate oncological management initiated.[31] Discontinuation of teduglutide treatment is also recommended if symptoms of IF (eg, weight loss, diarrhea, or vomiting) reoccur and if no other treatable condition can be identified and successfully managed. Treatment may also be discontinued if there are no signs of efficacy after 12 months.[2]

In adult patients, there are no data to indicate criteria on considering the discontinuation of teduglutide in patients in whom treatment was effective. The clinical effects of teduglutide diminish upon treatment cessation, and patients may experience dehydration, FE imbalance, and micronutrient deficiency if not adequately monitored.[1,2,32] For patients who only partially respond to teduglutide treatment, lifelong supplementation with IVS, enteral nutrition, and oral nutrition is anticipated.[65]

WEANING OFF IVS

Weaning off IVS is a complex process that should be individualized for each patient. It should only be attempted in patients in the stabilized phase of treatment, and patients should be very closely monitored during weaning off IVS to prevent destabilization.[17,19] Monitoring after the discontinuation of IVS should include an assessment of the items evaluated during teduglutide treatment initiation (ie, general health status; vital signs, body weight, body mass index, and body composition by bioimpedance analysis; energy and FE balances; oral intake of food, fluid, and other medications; urine and fecal output; and GI tract symptoms, such as diarrhea, abdominal pain, and nausea).[32,52,66] The algorithm implemented in STEPS,[30] based on changes in urinary volume output, reflects current clinical practice for IVS reduction and weaning (Table 5).[19]

Weaned patients still require long-term monitoring for nutrition deficits and may need specialized diets, vitamin/micronutrient supplementation, concomitant antidiarrheal and other medications (for symptomatic relief or treatment of other conditions), and fluid optimization (including occasional or intermittent intravenous rehydration, for example during seasonal outdoor temperature increases).[19,67] Long-term monitoring is needed to identify potential complications associated with SBS with intestinal insufficiency/deficiency, such as oxalate urolithiasis, bone-related issues, declining renal function, and liver disease, as well as GI polyps.[2,68] Importantly, once patients are weaned off IVS, treatment with teduglutide should be continued to maintain its beneficial effects.[2,29,32]

OPTIMAL HEALTHCARE SET-UP FOR THE MANAGEMENT OF SBS-IF

According to ESPEN guidelines, the complex individualized management of SBS-IF requires the expertise of several different specialist HCPs, including gastroenterologists, physicians with specialty or expertise in clinical nutrition, dietitians, nurses, pharmacists, and surgeons, working as a multidisciplinary team for the best clinical outcomes; management is ideally coordinated via centralized specialist care centers using established intestinal rehabilitation programs.[6,8,60,67,69,70] Furthermore, strengthening links between specialized IF centers and nonspecialized teams will give more patients the opportunity to receive appropriate treatment that is less dependent on their ability to access care in large regional healthcare settings.[67] For example, the Learn Intestinal Failure Tele-ECHO project uses regular web-based virtual clinics to link specialist teams at academic centers to primary care clinicians and other nonspecialists in local communities to increase their knowledge and expertise in IF and PN and so improve patient care.[71]

Although ESPEN guidelines recommend IVS as the primary treatment for patients with SBS-IF, early referral to specialist intestinal rehabilitation centers is also recommended to ensure timely treatment with hormonal intestinal growth factors as well as assessment of candidacy for intestinal transplantation in eligible patients.[72]

As hormonal intestinal growth factors are the newest medical option for the treatment of SBS-IF, studies are required to investigate the cost effectiveness of these drugs in patients affected by the more severe feature of SBS-IF who may also be considered candidates for a rehabilitative intestinal transplantation.

CONCLUSIONS

SBS-IF is a rare condition of the GI tract associated with comorbidities, and IVS is the mainstay of its treatment. Management of SBS-IF is complex, and the burden of SBS

itself and the IVS impairs the patient's HRQoL.[17,18] The goal of treatment for patients with SBS-IF is to maximize intestinal remnant absorptive capacity so the need for IVS support may eventually be reduced or eliminated.[16] Teduglutide treatment has been shown to be clinically effective in reducing IVS dependence and improving HRQoL in patients with SBS-IF.[16,26–28,31,40,46] Optimal use of teduglutide in patients with SBS-IF requires the provision of support and management guidance to HCPs, education of patients and management of their expectations, and identification of patients suitable for teduglutide treatment, followed by appropriate initiation of therapy (including prior stabilization of IVS) and continued regular monitoring. The complex and individualized management of SBS-IF requires the expertise of several different specialist HCPs working together in a multidisciplinary team who can also objectively evaluate the risk-benefit ratio of teduglutide treatment.[60] Specialized IF centers with multidisciplinary teams offer ongoing support and guidance for treating physicians and patients; links between specialized IF centers and nonspecialized teams should be formally established to give more patients the opportunity to receive the optimal treatments.

AUTHOR CONTRIBUTIONS

All authors participated in the conception, design, and structure of this manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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CONFLICT OF INTERESTS STATEMENT

Loris Pironi is a member of the Scientific Advisory Board for the SBS registry for Takeda and a member of advisory boards for HPN management for Baxter Italy. Johane P. Allard has received honoraria from Takeda as a consultant and speaker; research support from Takeda as a study site principal investigator; research support from OMS and from Fresenius Kabi as a principal investigator; honoraria from Baxter as a speaker and consultant; and research support from Zealand Pharma as a site principal investigator. Francisca Joly has served as a study investigator for NPS Pharmaceuticals, Inc., Takeda, VectivBio, and Zealand Pharma and as an advisory board member for Aguettant, Baxter Healthcare, B. Braun, Fresenius, Homeperf, Nestlé Health Sciences, TherAchon AG, Theradial, Takeda, VectivBio, and Zealand Pharma A/S. Elisabeth Genestin and Parnia Geransar are employees and stockholders of Takeda. Ulrich-Frank Pape is a member of the Scientific Advisory Board for the SBS registry for Takeda.

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