Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Disease-modifying therapies in short bowel syndrome

Brune de Dreuille and Francisca Joly

Abstract

Short bowel syndrome (SBS) is the main cause of chronic intestinal failure (IF), defined as 'the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth'. SBS is a rare disease requiring a multidisciplinary approach in specialized IF units. The aim of this review was to discuss the current pharmacological management of SBS-associated IF, since emerging treatments are currently modifying the natural evolution of these patients. Enterohormone therapy has become the first-choice treatment and may decrease the need for parenteral support and improve patients' quality of life.

Addresses

Department of Gastroenterology and Nutritional Support, Center for Intestinal Failure, Reference Centre of Rare Disease MarDI, AP-HP Beaujon Hospital, University of Paris Inserm UMR 1149, Paris, France

Corresponding author: Joly, Francisca (francisca.joly@aphp.fr)

Current Opinion in Pharmacology 2022, **65:**102240

This review comes from a themed issue on **Gastrointestinal (2022)**

Edited by **Tim Vanuystel** and **Pohl Daniel**

For complete overview about the section, refer Gastrointestinal (2022)

Available online 23 May 2022

https://doi.org/10.1016/j.coph.2022.102240

Introduction

Short bowel syndrome (SBS) is a rare disease resulting from extensive intestinal resection, and it is the main cause of chronic intestinal failure (IF) in adults.

IF is defined as "the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth", and can be classified into 3 subgroups: type I (acute, short-term condition), type II (prolonged acute condition) and type III (chronic condition) [1].

The causes of SBS are varied (e.g., mesenteric ischemia, Crohn's disease, radiation enteritis, surgical complications …), and mostly benign (patients with SBS secondary to radiation enteritis are in remission or cured of their cancer). The prevalence of this disease is not well known, in particular, because of its great variability between countries. However, the exact incidence of SBS from benign causes is estimated at 2/million/year [2].

The severity of SBS is related to its etiology, remnant small bowel length, and bowel anatomy after resection. Indeed, SBS can be divided into three anatomical subtypes (Figure 1): end jejunostomy, jejunocolic anastomosis (where part of the colon is in continuity with the remnant small bowel), and jejunoileal anastomosis (where the colon and the ileocecal valve are preserved) [3].

Intestinal resection may lead to IF that is managed with parenteral nutrition (PN), which provides energy, fluid, and electrolyte needs to patients.

Short bowel syndrome

Physiology and spontaneous adaptation

Following intestinal resection, several response mechanisms take place in patients in three phases:

- The **acute phase** (lasting about 4–6 weeks after resection), where gastric hypersecretion can result in diarrhea with important fluid and electrolyte loss. The challenge during this phase is to compensate dehydration and monitor the micro- and macronutrient deficiencies.
- The **adaptation phase** takes place up to 12–24 months after resection, and is characterized by the implementation of spontaneous adaptation mechanisms in SBS patients. The main mechanisms described are a morphological adaptation (hypertrophy of intestinal crypts), the onset of compensatory hyperphagia, a change in microbiota composition, and endocrine hormone production and secretion. All these physiological adaptations improve the energy, fluid, and electrolyte balances and may allow reducing or even weaning from PN [4,5].
- The **stationary phase** takes place after the spontaneous adaptation phase and several long-term complications can then appear (such as oxalate lithiasis in patients with colon in continuity) in addition to the risk of malnutrition and home parenteral nutrition (HPN) complications.

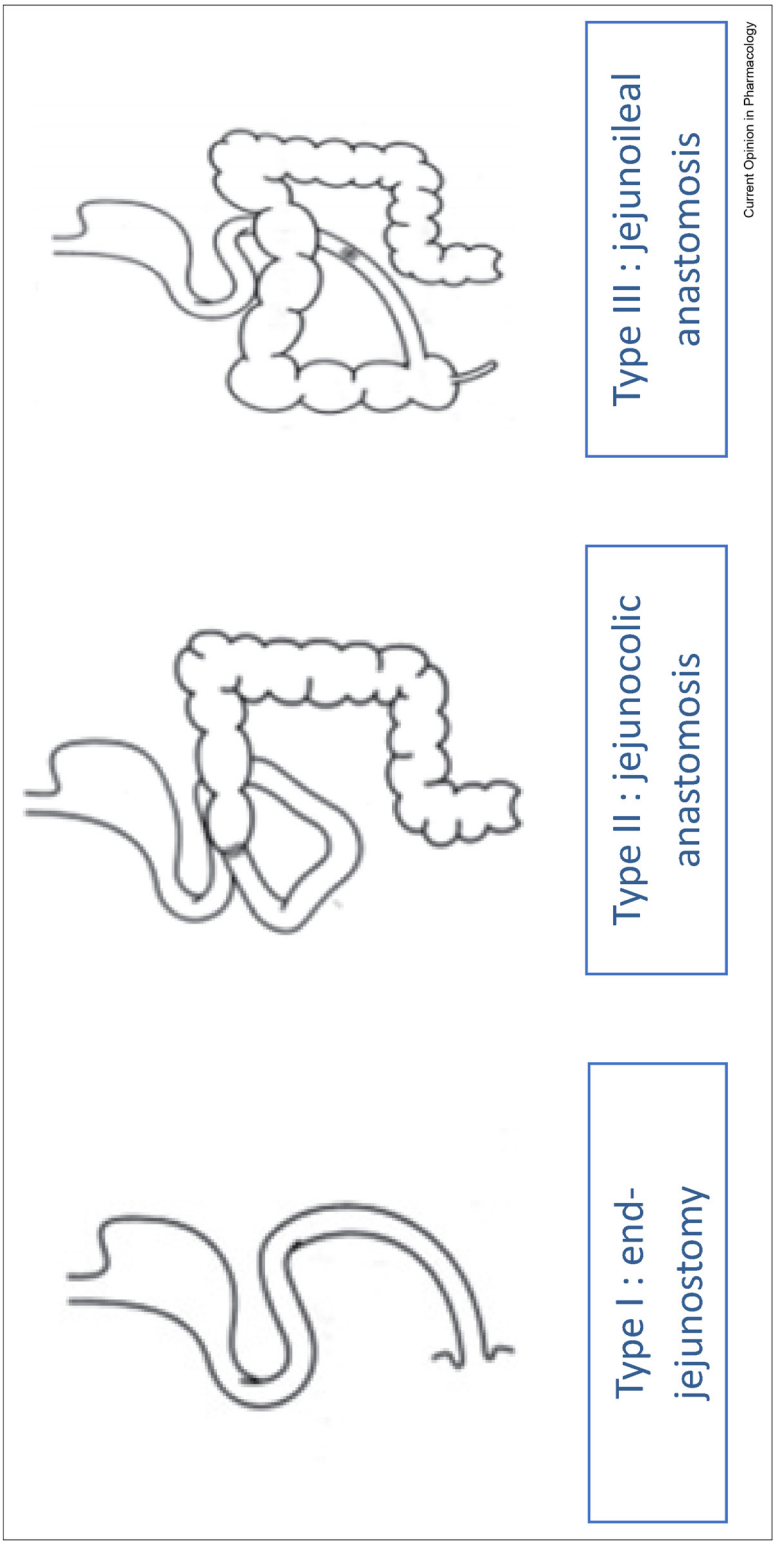


Figure 1

The three anatomic types of short bowel syndrome.

Prognosis depending on SBS anatomy, etiology, and functional loss

The survival rate of patients with SBS has been assessed in different cohorts and is around 90% at 1 year, 65% at 5 years, and 30% at 20 years. Most deaths occurring in the first two years of PN are due to the underlying disease or to pre-existing malignancies but not to HPN complications. Several factors that may influence patients' prognosis have been identified: Crohn's disease and chronic intestinal pseudo-obstruction leading to SBS have been associated with better survival, and the age of the patient inversely correlates with the survival rate [6,7].

Regarding HPN dependence, several characteristics of the patients may influence the natural evolution. Weaning from PN is a key factor for the prognosis of SBS patients because of the complications of long-term HPN, such as liver failure and catheter-related complications, and its negative impact on the quality of life (QoL).

Patients' dependence on PN depends on the absorptive function of the remnant gut, that is to say, its capacity to absorb nutrients and fluids, which is generally improved during the adaptation phase.

Furthermore, gastrointestinal (GI) reconstruction reduces the time to wean from PN, especially because of the important role of the colon in fluid and electrolyte absorption [6,7]. The gut anatomy also influences the degree of HPN dependence: a remnant small bowel length >75 cm and a colon length >57% reduce this dependence. More precisely, end-jejunostomy patients with a remnant small bowel <115 cm, jejunocolic anastomosis patients with a remnant small bowel <60 cm, and jejunoileal anastomosis patients with a remnant small bowel <35 cm are less likely to be weaned from PN [8].

Furthermore, patients receiving a large volume of PN or fluid and electrolyte supplementation alone are also less likely to be weaned from PN [9].

Thus, not only the underlying disease and the anatomy of the remnant bowel but also the mucosal function of the gut is important to determine the severity of IF as well as the prognosis of SBS patients.

Management of gastrointestinal symptoms

In addition to the spontaneous mechanisms observed in the bowel after resection, that may be beneficial to the patient, some GI symptoms may be managed with adequate treatment.

PN and dietetics

First, appropriate intravenous supplementation should be initiated after resection, based on the energy, fluid, and electrolyte needs, with micronutrient supplementation when necessary. In case of lipid malabsorption, supplementation with fat-soluble vitamins (A,D,E,K) may also be given [10]. Regarding the dietary management of GI symptoms, a hyperphagic diet is recommended. Patients are advised to take frequent and small meals (at least five), and to avoid overconsumption of fluids during meals. High-protein and high-calorie diet are recommended to compensate malabsorption [11].

For patients with colon in continuity, a high-carbohydrate, low-fat diet is recommended, as well as a low-oxalate diet to avoid oxaluria and nephrolithiasis [12]. On the other hand, patients with end-jejunostomy can benefit from a high-lipid diet and oral rehydration solutions [1,10].

Surgical options

As for the surgical management of SBS, restoring the digestive continuity should be considered in all patients with enterostomy, and performed whenever possible, 3–6 months after the last resection. As previously mentioned, this procedure increases SBS patients' survival and reduces HPN dependence, by optimizing the bowel anatomy in patients with colon in continuity [13]. The patient nutritional status should be optimized before the reconstruction surgery [14].

In SBS patients with life-threatening complications, intestinal transplantation may be considered as the last surgical option, but this procedure is rarely performed due to its high mortality rate.

Conventional medical management of GI symptoms

Besides the medical management of the initial cause of intestinal resection, some treatments are commonly used to reduce GI symptoms. Proton pump inhibitors (PPI) effectively reduce gastric hypersecretion occurring in the acute phase of SBS. In end-jejunostomy patients, this treatment must sometimes be continued for life, whereas in patients with colon in continuity, it can usually be discontinued after one year. Regarding the management of diarrhea, which is one of the most troublesome symptoms for patients, opioid drugs such as loperamide or codeine may effectively reduce transit time and thus reduce diarrhea [10,12].

Thus, the natural evolution of SBS after resection and the mechanisms underlying the physiological adaptations need to be understood since they are crucial for patients [4,5]. The factors associated with patients' survival and weaning from PN are well described and the management of these patients has improved significantly in the last few decades, notably through the advances in HPN management, leading to an amelioration in patients' QoL and survival.

However, the advent of new treatments derived from gut hormones has changed the management of SBS patients and challenged the knowledge of the spontaneous evolution of SBS.

Pharmacological management: a new place for growth factors

In recent years, GI peptide hormones have raised particular interest in the research and clinical management of SBS patients. Since their use could change the course of the disease, some of them are now part of the therapeutic arsenal, and others are under investigation.

Two proglucagon-derived enterohormones have been widely investigated, especially because of their trophic effect on the gut mucosa. Indeed, proglucagon gene encodes for 3 peptides, namely glucagon, GLP-1 and GLP-2, which share 40−50% sequence identity [15].

Glucagon-like peptide 1 (GLP-1)

The use of GLP-1 analogs has been assessed for the treatment of SBS patients, due to their effect on gastric emptying. The administration of exendin-4, a GLP-1 receptor agonist, and liraglutide, a GLP-1 analog, both approved for the treatment of type 2 diabetes, was tested in respectively 5 and 8 SBS patients, in an off-label use. These pilot studies have shown encouraging results, including a slowing of gastric emptying, a reduction in stoma output, and an improved absorption [16,17]. This important improvement observed in bowel absorption and nutritional status needs to be confirmed in larger studies [18,19].

Glucagon-like peptide 2 (GLP-2)

GLP-2 is another proglucagon-derived peptide secreted by the L-cells of the diffuse enteroendocrine system in response to nutrient ingestion. This endogenous hormone increases villus height and crypt depth, thus enhancing intestinal absorption. It also increases transit time and mesenteric blood flow and has a beneficial effect on the barrier function and immune protection [15,20].

Teduglutide is a GLP-2 analog resulting from the substitution of a single amino acid compared to endogenous GLP-2, allowing resistance to degradation by DDP-4, thus extending its half-life to 2 h.

Clinical trials

The results of Teduglutide human clinical trials (CTs) are summarized Table 1.

The first phase III trial has shown encouraging results in terms of treatment tolerance and efficacy. In this study, 86 patients were treated with Teduglutide (n = 43) or placebo (n = 43) for 24 weeks, and the number of responders was significantly higher in the Teduglutide group than in the placebo group, while the number of patients who discontinued treatment was similar between both groups. The response to treatment was defined as a 20% reduction in PN volume [21]. This study has allowed identifying a subpopulation of patients showing higher response rates to Teduglutide: the population with a mean age of 52 years, Crohn's disease as the most common etiology of SBS, and with a lower percentage of the remnant colon than the overall study population [22].

Some of the patients included in this 24-week study named STEPS (Study of Teduglutide Effectiveness in PN-Dependent SBS Subjects) then participated in the STEPS-II extension study. They were treated for 24 months with Teduglutide after the first 24 weeks of treatment with either placebo or Teduglutide. A total of 65 patients completed the study, and the preliminary results regarding treatment response and tolerance were confirmed. Thirteen patients were weaned from PN and most adverse events were mild to moderate [23].

The STEPS-III study has confirmed the long-term safety and efficacy of Teduglutide. Indeed, 13 patients were followed for 42 or 36 months (depending on the group to which they were assigned in the first part of the study). All patients previously weaned from PN remained PN-free and no serious adverse event was reported. However, all patients reported at least one treatment-emergent adverse event (TEAE), i.e., an asthenic condition and diarrhea in most cases, but none of these TEAEs led to treatment discontinuation [24].

These long-term studies aimed at determining whether some patients were more likely to respond to treatment.

Table 1

Summary of Teduglutide phase III clinical trials.

Phase III study	Authors	Number of patients	Teduglutide dose	Study duration	Response to treatment	Weaning off PN	Number of treatment discontinuations
STEPS-I	Jeppesen et al. (2012)	n = 43 Teduglutide n = 43 placebo	0.05 mg/kg/day	24 weeks	63% (n = 27)	0	n = 2
STEPS-II	Schwartz et al. (2016)	n = 65	0.05 mg/kg/day	24 months	74% (n = 48)	20% (n = 13)	n = 0
STEPS-III	Seidner et al. (2018)	n = 13	0.05 mg/kg/day	36 months	Non-specified	31% (n = 4)	n = 0

Regarding bowel anatomy, the reduction in PN volume was greater in end-jejunostomy patients than in jejunocolic anastomosis patients, and this could be due to the fact that they received higher PN volume at baseline. Overall, the response to Teduglutide has been associated with the bowel anatomy, SBS features, and the initial prescription of PN [25].

Real-world data

After the aforementioned CTs and the approval of Teduglutide for SBS treatment, several real-world studies have been conducted. The characteristics and results of these studies are summarized in Table 2. Overall, a response rate of at least 70% was achieved in these cohorts, and 15−61% of patients could be weaned from PN. The presence of a colon in continuity has been shown to be a favorable factor for achieving weaning from PN, as well as a small initial volume of PN and a significant oral intake [26,27].

Identification of predictors of response

Early responders tend to have no colon in continuity, and Crohn's disease seems to be the main cause of SBS in this subgroup. On the other hand, late responders would be more likely to have colon in continuity and ileocecal valve [28]. Joly et al. have reported their real-life experience with teduglutide in a French national multicenter (10 expert centers), retrospective trial (n = 54). This is the largest real-world cohort published to date. After 24 weeks of treatment, 13 patients (24%) were completely weaned from parenteral support (PS) and 46 patients (85%) were responders (reduction in PS volume >20% from baseline). A higher basal oral intake was associated with a response at week 24 (P = 0.02). However, no association was found with the age, the underlying disease, and bowel anatomy. Furthermore, patients who were weaned from PS at week 24 received a lower volume of basal PS (P = 0.03), higher oral intake (hyperphagia) (P = 0.01), and had a remaining colon in continuity (P = 0.04) [26].

It is important to note that the clinical characteristics of the patients included in real-world studies as well as the outcomes reached with Teduglutide were not necessarily identical to those of the CTs. This is mainly due to the difference in the selection of patients (to be included in CTs, patients had to have a minimum of 3 PN perfusions a week, whereas in real-world the inclusion is larger, with no limit of perfusions), and to the PN reduction process used. Indeed, in CTs, a precise algorithm is used to reduce PN, based on the estimation of hydro-electrolytic absorption, whereas in real-world other factors are involved in the decision, such as weight, food intake, general status, and energy absorption.

A longer study in 18 patients with a mean follow-up of 3.2 years has failed to identify factors significantly associated with the response in terms of bowel anatomy and initial PN volume. In all PN-weaned patients, Crohn's disease was the cause of SBS and the ileocecal valve was absent [29]. After a thorough review of all the studies, it seems that the gut anatomy probably plays a pivotal role. Although the absolute reduction in PS volume was greater in patients with jejunostomy compared to those with colon in continuity, fewer jejunostomy patients were completely weaned from PS. It is therefore crucial to dissociate hydroelectrolytic/fluid dependence from energy dependence.

In order to find a way to monitor the clinical response to Teduglutide, a CT-scan study has been conducted in 31 SBS patients and has shown a significant increase in intestinal wall thickness less than 6 months after treatment initiation. Patients who achieved a reduction in PN volume ≥20% at 12 months tended to have a greater increase in wall thickness. Thus, imaging could be a useful tool to monitor the response to Teduglutide [30]. Further studies are needed to investigate the early monitoring.

Indications

Regarding treatment indications, patients could be classified as non-candidates (patients with a specific contraindication or on the waiting list for an intestinal transplant), potential candidates (patients with severe comorbidities and/or at risk of malignancies), for whom the potential initiation of treatment should be discussed carefully, and direct candidates without specific comorbidities or contraindications [31]. The specific

Table 2

Summary of Teduglutide real-world studies and results.

Authors	Number of patients	Teduglutide dose	Study duration	Response to treatment	Weaning off PN	Number of treatment discontinuations
Lam K et al. (2018)	n = 18	0.05 mg/kg/day	10 months	88% (n = 16)	61% (n = 11)	n = 0
Schoeler et al. (2018)	n = 14	Non-specified	24 months	71% (n = 10)	14% (n = 2)	n = 0
Noelting et al. (2019)	n = 20	Non-specified	12 months	82% (n = 16)	33% (n = 6)	n = 2
Pevny S et al. (2019)	n = 19	0.05 mg/kg/day	12 months	79% (n = 15)	21% (n = 4)	n = 10
Joly F et al. (2019)	n = 54	0.05 mg/kg/day	6 months	85% (n = 46)	24% (n = 13)	n = 2
Puello et al. (2020)	n = 18	0.05 mg/kg/day	36 months	88% (n = 16)	28% (n = 5)	n = 5

Table 3

Teduglutide contraindications (from REVESTIVE® Product Monograph, Shire-NPS Pharmaceuticals).

Revestive is contraindicated for patients who:
Are hypersensitive to this drug or to any ingredient in the formulation, including any nonmedicinal ingredient, or component of the container.
Have active gastrointestinal (GI) malignancy (GI tract, hepatobiliary, pancreatic)
Have a history of malignancies in the gastrointestinal tract and/or the hepatobiliary system including pancreas within the last 5 years

contraindications to Teduglutide therapy issued by the manufacturer are listed Table 3. For potential candidates, initiation of treatment is questionable because of the comorbidities, especially cardiac insufficiencies, which are not specific contraindications but the efficacy of treatment could lead to adverse effects such as fluid overload. Moreover, patients who had radiotherapy in the past are at high risk of malignancies secondary to radiotherapy, thus they present a predisposing ground to secondary proliferative adverse effects of Teduglutide. For these 2 groups of patients, Teduglutide initiation should be decided on a case-by-case basis, and if initiated the patient's monitoring may be reinforced according to its condition.

For carefully selected patients, Teduglutide is the first-choice treatment, and it should be initiated during the adaptative or stationary phase, usually after at least one year of PN after resection.

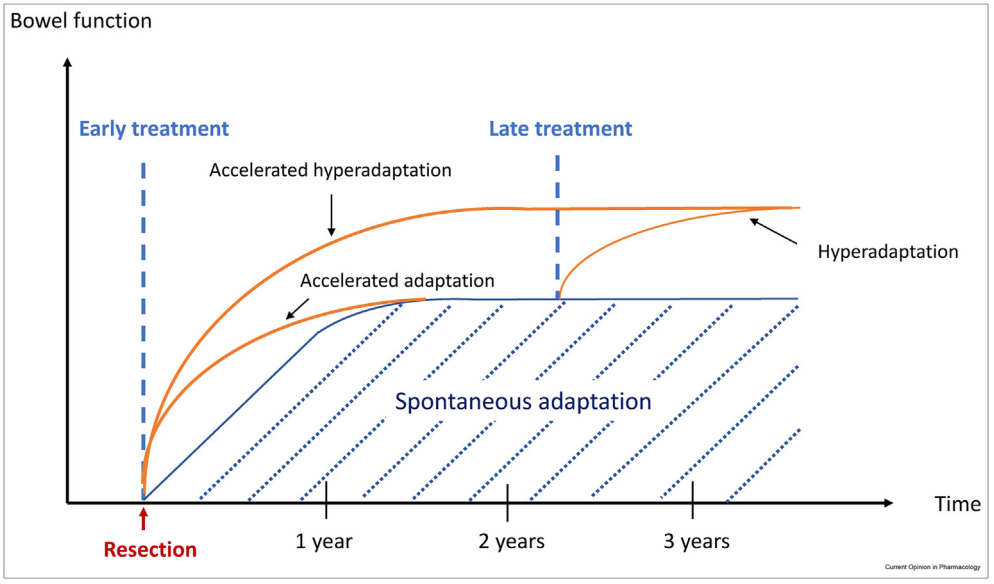
A definition of Teduglutide indication could in fact be the ongoing IF requiring continuation of PN even after one year of spontaneous adaption.

However, the time to treatment initiation is still discussed. A case report has described the case of a 37-year-old man with Crohn's disease leading to SBS with end-ileostomy after several resections, who initiated Teduglutide before intestinal continuity restoration. He was weaned from PN after 2 months and remained PN-free after surgery [32]. This type of study raises the question of treatment temporality. As schematically represented in Figure 2, it has not yet been determined whether early treatment could accelerate adaptation to reach earlier the rate of natural adaptation (plateau phase), or if it could rapidly induce a hyper-adaptation after resection, reaching a higher plateau phase than that reached spontaneously [33].

Impact on the quality of life

One of the most important goals in the management of patients with SBS-IF is to improve their QoL that is usually impaired either due to the burden of PS, complications of HPN, the presence of stoma, opiate use, symptoms of malabsorption, or the underlying disease [34,35]. The latest available data were published in 2020 from the STEPS trial in which the QoL was assessed using a validated SBS-QoL scale at baseline and every 4 weeks for a total of 24 weeks. The impact of teduglutide

Figure 2



Schematic presentation of intestinal adaptation and treatment. Adapted from Jeppesen et al. [33].

on SBS-related QoL compared to placebo varied between subgroups and was significant and more pronounced in patients who received the highest baseline volume of PS or with inflammatory bowel disease [36].

Tolerance and safety

Besides the proven efficacy of treatment, its tolerance and safety have been comprehensively assessed [26,37,38]. Although most reported adverse events were mild, the most common being abdominal pain, the lack of evidence does not currently allow deciding on the long-term safety of treatment. In particular, the risk of Teduglutide-induced neoplasia is still under investigation and should be taken into account for each patient. Indeed, several cases of unexpected small bowel polyps have been described in the literature in patients treated with Teduglutide [39,40], and in a study conducted in a large cohort of 170 SBS patients treated with Teduglutide, 5.8% of patients (n = 10) experienced colon polyps [41]. A prospective, observational, multi-center registry has been initiated in June 2014 to assess, among other outcomes, the risk of developing benign neoplasia [42].

Other GLP-2 analogs under development

Given the efficacy of this first GLP-2 analog, other GLP-2 analogs with longer half-lives are under clinical development.

Glepaglutide, another longer-acting GLP-2 analogue, is currently tested in a phase III clinical trial. The results of a single-center, phase II trial have already been published. A total of 18 patients were randomized to 3 treatment doses (0.1, 1, and 10 mg). Patients were treated for two 3-weeks periods separated by a washout period of 4–8 weeks. Endpoints included scintigraphy, wireless motility capsule, and paracetamol absorption test. In the 10-mg dose group (n = 9), Glepaglutide significantly increased the time to 10% gastric emptying (GE) of solids by 27 (4–50) minutes (adjusted mean [95% CI]), time to 50% GE of fluids by 40 (1–80) minutes, and time to 10% small bowel-emptying of solids by 21 (1–41) minutes. The wireless motility capsule transit did not significantly change in any of the dose groups [43].

Apraglutide is another GLP-2 analog under development, characterized by the substitution of 4 amino acids, and a very low clearance as shown *in vivo* in rats [44], allowing injecting patients once a week. In a placebo-controlled, double-blind, randomized, crossover phase 2 trial, eight adults with SBS-IF were treated with 5 mg of Apraglutide and placebo once a week for 4 weeks, followed by 10 mg of Apraglutide once a week for 4 weeks, with a washout period of 6–10 weeks between treatments. Safety was the primary endpoint. The safety profile was comparable for both doses. Treatment with 5 and 10 mg of Apraglutide once a week significantly increased the mean adjusted urine output by 714 mL/day (95% CI, 490–939; $P < 0.05$) and 795 mL/day (95% CI, 195–1394; $P < 0.05$), respectively, compared to placebo, without any significant difference between both doses [45].

These two molecules have longer plasma half-lives than Teduglutide, reaching around 50 h for Glapaglutide and 72 h for Apraglutide [45,46]. Pharmacokinetic studies have been conducted in rats to compare the pharmacological characteristics of the three GLP-2 analogs. The clearance of Apraglutide (0.27 ± 0.04) was lower than that of Glepaglutide (2.8 ± 0.4), Teduglutide (9.9 ± 2.1), and native GLP-2 (25 ± 2.3) [44].

Other discussed treatment options

In addition to the PN reduction elicited by GLP-2 analogs, reducing the stoma output could further improve patients' QoL. For this reason, the combination of the effects of GLP-1 and GLP-2 has been investigated. Dapiglutide is a new dual GLP-1 and GLP-2 receptor agonist, that has been tested in mice after intestinal resection. The results showed improved glucose tolerance and intestinal growth, associated with reduced transit time and water loss [47].

With a similar objective, a pilot study has assessed the effect of Sitagliptin, a DDP-4 inhibitor, in SBS patients. This molecule would prevent the degradation of GLP-1 and GLP-2 by DDP-4. This small study has failed to show any improvement in intestinal absorption but a heterogenous response has been observed [48].

Thus, combining the trophic effects of GLP-2 and the GI motility benefits of GLP-1 could be beneficial in the treatment of SBS patients in the future.

Conclusion

SBS is a rare complex disorder due to multiple etiologies, that requires a multidisciplinary management. PN is the reference treatment in patients with chronic IF due to SBS and can lead to several long-term complications in addition to a significantly impaired QoL. The advent of GLP-2 analogs that may change the prognosis of patients is adding a new dimension to the pharmacological management of SBS. Enterohormone therapy is undoubtedly the new cornerstone in SBS-IF. Based on the results of randomized controlled trials and recent real-world experience, Teduglutide appears to be very effective. However, careful monitoring of patients during treatment is mandatory and the results of ongoing studies are promising for patients. A new era has just begun with the identification of key hormones for the management of SBS-IF. Therefore, new enterohormone analogs are currently being developed and studied to combine prototrophic, proabsorptive, and motility effects with extended half-life. These advances will also allow assessing their potential, especially in

combination with other enterohormones. Since this new therapy completely modifies the natural course of SBS, patients' care should be adjusted accordingly and these new drugs should be considered as part of a global strategy including dietetic, surgical, and nutritional approaches.

Funding

This manuscript has not been funded.

Conflict of interest statement

B.D. received a grant from Takeda for the implementation of a clinical study.
F.J. has participated in NPS Pharmaceuticals' Scientific, Shire's Advisory Board, Takeda, Zealand and Vectibio advosiry boards and in randomized controlled clinical trials of teduglutide supported by NPS and takeda, and randomized controlled clinical trials for Zealand (for Glepaglutide) and Vectivbio (Apraglutide).

Writing assistance

Sophie Pégorier.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen P, Joly F, Kelly D, Lal S, Staun M, *et al.*: **ESPEN guidelines on chronic intestinal failure in adults**. *Clin Nutr* 2016, **35**.
2. Pironi L: **Intestinal failure in adults: recommendations from the ESPEN expert groups**. *Clin Nutr* 2018, **37**:1798–1809.
3. Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud J-C, Matuchansky C: **Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome**. *Gastroenterology* 1999, **117**:1043–1050.
4. Tappenden KA: **Intestinal adaptation following resection**. *J Parenter Enteral Nutr* 2014, **38**:23S–31S.
5. Le Beyec J, Billiauws L, Bado A, Joly F, Le Gall M: **Short bowel syndrome: a paradigm for intestinal adaptation to nutrition?** *Annu Rev Nutr* 2020, **40**:299–321.
6. Joly F: **Five-year survival and causes of death in patients on home parenteral nutrition for severe chronic and benign intestinal failure**. *Clin Nutr* 2018, **37**:1415–1422.
7. Dibb M, Soop M, Teubner A, Shaffer J, Abraham A, Carlson G, Lal S: **Survival and nutritional dependence on home parenteral nutrition: three decades of experience from a single referral centre**. *Clin Nutr* 2017, **36**:570–576.
8. Amiot A, Messing B, Corcos O, Panis Y, Joly F: **Determinants of home parenteral nutrition dependence and survival of 268 patients with non-malignant short bowel syndrome**. *Clin Nutr* 2013, **32**:368–374.
9. Pironi L, Steiger E, Joly F, Wanten GJA, Chambrier C, Aimasso U, Sasdelli AS, Szczepanek K, Jukes A, Theilla M, *et al.*: **Intravenous supplementation type and volume are associated with 1-year outcome and major complications in patients with chronic intestinal failure**. *Gut* 2020, **69**:1787–1795.
10. Hollanda Martins Da Rocha M, Lee ADW, Marin MLDM, Faintuch S, Mishaly A, Faintuch J: **Treating short bowel syndrome with pharmacotherapy**. *Expet Opin Pharmacother* 2020, **21**:709–720.
11. Billiauws L, Maggiori L, Joly F, Panis Y: **Medical and surgical management of short bowel syndrome**. *J Vis Surg* 2018, **155**:283–291.
12. Massironi S, Cavalcoli F, Rausa E, Invernizzi P, Braga M, Vecchi M: **Understanding short bowel syndrome: current status and future perspectives**. *Dig Liver Dis* 2020, **52**:253–261.
13. Aubert M, Mege D, Billiauws L, Joly F, Panis Y: **State-of-the-art colorectal disease: conservative surgical management of intestinal failure in adults**. *Int J Colorectal Dis* 2021, **36**:1597–1607.
14. Nikoupour H, Theodorou A, Arasteh P, Lurje G, Kalff JC, von Websky MW: **Update on surgical management of enteroatmospheric fistulae in intestinal failure patients**. *Curr Opin Organ Transplant* 2022, **27**:137–143.
15. Brubaker PL: **Glucagon-like peptide-2 and the regulation of intestinal growth and function**. *Compr Physiol* 2018, **8**:26.
16. Kunkel D, Basseri B, Low K, Lezcano S, Soffer EE, Conklin JL, Mathur R, Pimentel M: **Efficacy of the glucagon-like peptide-1 agonist exenatide in the treatment of short bowel syndrome**. *Neuro Gastroenterol Motil* 2011, **23**:7.
17. Hvistendahl M, Brandt CF, Tribler S, Naimi RM, Hartmann B, Holst JJ, Rehfeld JF, Hornum M, Andersen JR, Henriksen BM, *et al.*: **Effect of liraglutide treatment on jejunostomy output in patients with short bowel syndrome: an open-label pilot study**. *J Parenter Enteral Nutr* 2016, https://doi.org/10.1177/0148607116672265.
18. Billiauws L, Joly F: **Emerging treatments for short bowel syndrome in adult patients**. *Expet Rev Gastroenterol Hepatol* 2019, **13**:241–246.
19. Hunt JE, Holst JJ, Jeppesen PB, Kissow H: **GLP-1 and intestinal diseases**. *Biomedicines* 2021, **9**:383.
20. Daoud DC, Joly F: **The new place of enterohormones in intestinal failure**. *Curr Opin Clin Nutr Metab Care* 2020, **23**:6.
21. Jeppesen PB: **Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure**. *Gastroenterology* 2012, **143**:12.
22. Chen KS, Xie J, Tang W, Zhao J, Jeppesen PB, Signorovitch JE: **Identifying a subpopulation with higher likelihoods of early response to treatment in a heterogeneous rare disease: a post hoc study of response to teduglutide for short bowel syndrome**. *Therapeut Clin Risk Manag* 2018, **14**:1267–1277.
23. Schwartz LK, O'Keefe SJD, Fujioka K, Gabe SM, Lamprecht G, Pape U-F, Li B, Youssef NN, Jeppesen PB: **Long-term teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome**. *Clin Transl Gastroenterol* 2016, **7**:e142.
24. Seidner DL, Fujioka K, Boullata JI, Iyer K, Lee H-M, Ziegler TR: **Reduction of parenteral nutrition and hydration support and safety with long-term teduglutide treatment in patients with short bowel Syndrome–Associated intestinal failure: STEPS-3 study**. *Nutr Clin Pract* 2018, **33**:520–527.
25. Jeppesen PB: *Factors associated with response to teduglutide in patients with short-bowel syndrome and intestinal failure*. 2018.
26. * Joly F, Seguy D, Nuzzo A, Chambrier C, Beau P, Poullenot F, Thibault R, Armengol Debeir L, Layec S, Boehm V, *et al.*: **Six-month outcomes of teduglutide treatment in adult patients with short bowel syndrome with chronic intestinal failure: a real-world French observational cohort study**. *Clin Nutr* 2020, **39**:2856–2862.
This is the first French real-life cohort study on the efficacy of Teduglutide treatment in SBS patients, showing that 85% of the patients responded to treatment and 24% of them were able to discontinue parenteral nutrition.

27. Lam K, Schwartz L, Batisti J, Iyer KR: **Single-center experience with the use of teduglutide in adult patients with short bowel syndrome**. *J Parenter Enteral Nutr* 2018, **42**:225–230.

28. * Chen K, Joly F, Mu F, Kelkar SS, Olivier C, Xie J, Seidner DL: **Predictors and timing of response to teduglutide in patients with short bowel syndrome dependent on parenteral support**. *Clin Nutr ESPEN* 2021, **43**:420–427.

This study addresses the timing of response to Teduglutide, and the authors demonstrate that some clinical features are associated with an earlier response (inflammatory bowel disease as a cause of SBS, the presence of a stoma and the absence of the ileocecal valve). Such findings could lead to an improve in SBS patients' management.

29. Puello F, Wall E, Herlitz J, Lozano ES, Semrad C, Micic D: **Long-term outcomes with teduglutide from a single center**. *J Parenter Enteral Nutr* 2021, **45**:318–322.

30. Martin A, Boehm V, Zappa M, Billiauws L, Bonvalet F, Nuzzo A, Vilgrain V, Joly F, Ronot M: **Imaging as predictor of clinical response to teduglutide in adult patients with short bowel syndrome with chronic intestinal failure**. *Am J Clin Nutr* 2021, **113**:1343–1350.

31. Pironi L, Sasdelli AS, Venerito FM, Musio A, Pazzeschi C, Guidetti M: **Candidacy of adult patients with short bowel syndrome for treatment with glucagon-like peptide-2 analogues: a systematic analysis of a single centre cohort**. *Clin Nutr* 2021, **40**:4065–4074.

32. Schlager L, Stift A, Gartner J, Hütterer E, Harpain F: **Bridging intestinal failure with Teduglutide – a case report**. *Int J Surg Case Rep* 2021, **86**:106270.

33. Jeppesen PB: **Growth factors in short-bowel syndrome patients**. *Gastroenterol Clin N Am* 2007, **36**:109–121.

34. Carlsson E, Bosaeus I, Nordgren S: **Quality of life and concerns in patients with short bowel syndrome**. *Clin Nutr* 2003, **22**:445–452.

35. Kalaitzakis E, Carlsson E, Josefsson A, Bosaeus I: **Quality of life in short-bowel syndrome: impact of fatigue and gastrointestinal symptoms**. *Scand J Gastroenterol* 2008, **43**:1057–1065.

36. Chen K, Mu F, Xie J, Kelkar SS, Olivier C, Signorovitch J, Jeppesen PB: **Impact of teduglutide on quality of life among patients with short bowel syndrome and intestinal failure**. *J Parenter Enteral Nutr* 2020, **44**:119–128.

37. Pape U-F, Iyer KR, Jeppesen PB, Kunecki M, Pironi L, Schneider SM, Seidner DL, Lee H-M, Caminis J: **Teduglutide for the treatment of adults with intestinal failure associated with short bowel syndrome: pooled safety data from four clinical trials**. *Ther Adv Gastroenterol* 2020, **13**, 175628482090576.

38. Kochar B, Long MD, Shelton E, Young L, Farraye FA, Yajnik V, Herfarth H: **Safety and efficacy of teduglutide (gattex) in patients with Crohn's disease and need for parenteral support due to short bowel syndrome–associated intestinal failure**. *J Clin Gastroenterol* 2017, **51**:508–511.

39. Ukleja A, Alkhairi B, Bejarano P, Podugu A: **De novo development of hamartomatous duodenal polyps in a patient with short bowel syndrome during teduglutide therapy: a case report**. *J Parenter Enteral Nutr* 2017, https://doi.org/10.1177/0148607117718480.

40. * Pevny S, Pape U, Elezkurtaj S, Rieger A, Jürgensen C, Blüthner E, Jochum C, Tacke F, Maasberg S: **De novo development of distal jejunal and duodenal adenomas after 41 Months of teduglutide treatment in a patient with short-bowel syndrome: a case report**. *J Parenter Enteral Nutr* 2021, **45**:652–656.

This case report describes the development of jejunal and duodenal adenomas in a patient with SBS after 41 months of Teduglutide treatment. This raises awareness about the importance of monitoring with upper endoscopies during treatment with Teduglutide.

41. Loutfy A, Kurin M, Shah R, Davitkov P: **Characterization of American teduglutide consumers from 2015 to 2020: a large database study**. *J Parenter Enteral Nutr* 2021, https://doi.org/10.1002/jpen.2221.

42. Shire: *A prospective, multi-center registry for patients with short bowel syndrome*. clinicaltrials.gov; 2021.

43. Hvistendahl MK, Naimi RM, Enevoldsen LH, Madsen JL, Fuglsang S, Jeppesen PB: **Effect of Glepaglutide, a long-acting glucagon-like peptide-2 analog, on gastrointestinal transit time and motility in patients with short bowel syndrome: findings from a randomized trial**. *JPEN - J Parenter Enter Nutr* 2020, **44**:1535–1544.

44. Hargrove DM, Alagarsamy S, Croston G, Laporte R, Qi S, Srinivasan K, Sueiras-Diaz J, Wiśniewski K, Hartwig J, Lu M, *et al.*: **Pharmacological characterization of Apraglutide, a novel long-acting peptidic glucagon-like peptide-2 agonist, for the treatment of short bowel syndrome**. *J Pharmacol Exp Therapeut* 2020, **373**:193–203.

45. ** Eliasson J, Hvistendahl MK, Freund N, Bolognani F, Meyer C, Jeppesen PB: **Apraglutide, a novel glucagon-like peptide 2 analog, improves fluid absorption in patients with short bowel syndrome intestinal failure: findings from a placebo-controlled, randomized phase 2 trial**. *J Parenter Enteral Nutr* 2021, https://doi.org/10.1002/jpen.2223.

This phase II trial demonstrates safety and efficacy of Apraglutide (on the criterion of an increased intestinal fluid absorption), thus opening the possibility for a new long-acting GLP-2 analog for the treatment of SBS.

46. Naimi RM: *Effects of glepaglutide, a novel long-acting glucagon-like peptide-2 analogue, on markers of liver status in patients with short bowel syndrome: findings from a randomised phase 2 trial*. 2019.

47. Reiner J, Berlin P, Held J, Thiery J, Skarbaliene J, Griffin J, Russell W, Eriksson P, Berner-Hansen M, Ehlers L, *et al.*: **Dapiglutide, a novel dual GLP-1 and GLP-2 receptor agonist, attenuates intestinal insufficiency in a murine model of short bowel**. *J Parenter Enteral Nutr* 2021, https://doi.org/10.1002/jpen.2286.

48. Naimi RM, Hvistendahl MK, Thomassen LM, Johnsen H, Christiansen CB, Holst JJ, Hartmann B, Jeppesen PB: **Sitagliptin, a dipeptidyl peptidase-4 inhibitor, in patients with short bowel syndrome and colon in continuity: an open-label pilot study**. *BMJ Open Gastroenterol* 2021, **8**, e000604.