Review

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
50(3) 1–10
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DOI: 10.1177/03000605221086145
journals.sagepub.com/home/imr
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An updated overview of glucagon-like peptide-2 analog trophic therapy for short bowel syndrome in adults

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Abstract

Short bowel syndrome (SBS) is a clinical condition characterized by a failure to achieve optimal intestinal adaptation, which is necessary to maintain oral/enteral autonomy. At present, the treatment options for SBS are primarily intestinal replacement and rehabilitation. Intestinal rehabilitation mainly includes non-transplantation surgery and intestinal rehabilitation measures. In recent years, intestinal rehabilitation in patients with SBS using nutritional intestinal hormones, especially glucagon-like peptide-2 analogs, has made great progress. Many high-quality studies have provided evidence-based medical findings to support the development of clinical guidelines. This article reviews the latest research advancements regarding the use of glucagon-like peptide-2 analogs (teduglutide, glepaglutide, and apraglutide) in the treatment of SBS.

Keywords

Short bowel syndrome, glucagon-like peptide-2 analog, teduglutide, glepaglutide, apraglutide, gastrointestinal, rehabilitation, trophic therapy

Date received: 24 May 2021; accepted: 21 February 2022

Introduction

Short bowel syndrome (SBS) is a rare and potentially life-threatening malabsorptive condition caused by a significant loss of functional bowel mass (secondary to congenital defects or disease-associated loss of absorption) or physical bowel mass (secondary to extensive intestinal resection).

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SBS is the most common cause of chronic intestinal failure,[5] accounting for approximately 75% of cases of chronic intestinal failure in adults and 50% such events in children.[6]

Intestinal rehabilitation therapy, especially medication therapy, plays an important role in the treatment of SBS, and it is also a vital strategy before intestinal replacement techniques, such as small bowel transplantation. Its theoretical basis is intestinal adaptation, which is mainly manifested in the enhancement of intestinal absorption function, increased secretion of intestinal absorption-stimulating hormones, an increase in appetite, and the corresponding changes in intestinal microecology. Some patients can be weaned off parenteral nutrition (PN), and they recover intestinal self-reliance through intestinal rehabilitation. In recent years, research on medication, especially intestinal hormone analogs such as glucagon-like peptide 2 (GLP-2) analogs, has made a great progress, expanded clinicians' understanding of nutritional intestinal hormones, and provided strong support for the formulation of treatment guidelines for patients with SBS.

Thus, this review article summarized current knowledge on the use of GLP-2 analogs in the treatment of SBS using the search terms GLP-2 analogs AND intestinal rehabilitation, teduglutide (TED) AND intestinal rehabilitation, glepaglutide (GLE) AND intestinal rehabilitation, apraglutide (APRA) AND intestinal rehabilitation, and short bowel syndrome AND intestinal rehabilitation.

GLP-2 and its analogs

Human GLP-2 (hGLP-2) is a systemic nutrient peptide hormone derived from proglucagon. It contains 33 amino acids; it is expressed, transcribed, and translated from the glucagon motif; and it is secreted by L-type endocrine cells in the distal small intestine and colon. GLP-2 can induce the proliferation of intestinal crypt cells, inhibit the apoptosis of intestinal epithelial cells and gastric acid secretion, promote the repair of damaged intestinal mucosa and absorption of intestinal nutrients, enhance the intestinal blood supply, delay gastric wall peristalsis, and regulate intestinal mucosal barrier function.[8–10] Compared with hGLP-2, GLP-2 analogs contain one or more substitutes for specific components of natural peptides; additionally, they both retain the pharmacological activity of natural GLP-2 and exhibit a more stable structure, longer half-life, and stronger bonding with targets.[11] Among the three analogs, TED has been approved for clinical use, whereas GLE and APRA still in the experimental stage.

TED

GLP-2 is easily removed by dipeptidyl peptidase IV in the kidneys, and it has an extremely short circulating half-life (approximately 7 minutes in humans), which greatly limits its therapeutic value.[12–15] TED is a GLP-2 analog in which an alanine in the natural peptide is replaced by glycine, eliminating the degradation site of dipeptidyl peptidase IV. The terminal half-life is 3.0 to 5.5 hours via the subcutaneous route in humans,[16,17] and its specificity for the GLP-2 receptor is similar to that of natural hGLP-2. In 2016, the European Society for Clinical Nutrition and Metabolism recommended that TED as the first-choice drug for nutritional intestinal hormone therapy in patients with SBS, and the evidence-based medical findings were moderately supportive.[18]

In 2005, an open-label phase II clinical trial was performed to evaluate the safety and efficacy of TED for the treatment of SBS.[19] TED significantly increased intestinal absolute and relative wet weight absorption, urine weight, and urinary sodium

excretion and decreased fecal wet weight and fecal energy excretion. The villus height, crypt depth, and mitotic index were significantly increased in patients with type I SBS. These changes were not observed after drug withdrawal. The side effects included enlargement of the stomal papilla and mild leg edema. Subsequently, many researchers have verified the aforementioned results and conducted in-depth explorations on this topic. The most famous project is the series of studies focused on TED effectiveness in PN-dependent SBS subjects (STEPS). Related analytical studies have addressed the reduction of PN dependence, the probability of ending PN, the duration of administration, withdrawal reactions, side effects, improvement in quality of life, cost–benefit ratios, treatment considerations, and the necessity of regular monitoring.

STEPS: In 2011, the first phase III TED study, dubbed STEPS (nct00798967; eudract 2008-006193-15), assessed the probability of ending PN in patients with SBS treated with TED.[20] The study included 43 patients each in the TED and placebo groups. The study revealed that the effective rate [63% (27/43) vs. 30% (13/43), $P = 0.002$], the mean reduction of PN [4.4 ± 3.8 L/week vs. 2.3 ± 2.7 L/week, $P < 0.001$], and the days off PN per week) [≥ 1 day; 54% (21/39) vs. 23% (9/39), $P = 0.005$] were significantly higher in the TED group than in the placebo group. TED also increased the plasma citrulline concentration. There was no significant difference in side effects between the two groups.

STEPS-2: The 2-year STEPS-2 study (nct00930644; eudract 2009-011679-65) evaluated the long-term safety and effectiveness of TED.[21] Based on the STEPS study, some new patients with SBS who had never received TED were included in this study. The patients were divided into three groups based on their treatments before admission: TED/TED group (treated with TED in both STEPS and STEPS-2), placebo/TED group (treated with placebo in STEPS and TED in STEPS-2), and no treatment/TED group (no treatment prior to receiving TED in STEPS-2). All patients received TED (0.05 mg/kg per day) via subcutaneous injection. The first group was enrolled for 30 months, and the latter two groups were enrolled for 24 months. The effective rate (>20% decrease in PNvolume by from baseline) was 65% (57/88), and the rates in the TED/TED, placebo/TED, and no treatment/TED groups were 89% (33/37), 46% (18/39), and 50% (6/12), respectively. The average volume reductions of PS in the three groups were 59%, 25%, and 19%, respectively. The duration of PN infusion was reduced by 1 day per week in 38 patients. Thirteen patients were weaned off PN, including three patients with type I SBS and 10 patients with type II or III SBS. The baseline requirement of PN in these patients was 3.5 to 13.4 L/week, and some patients were dependent on PN for 15 years. During the 30 months of TED treatment, the demand for PS continued to decline steadily, and the health and nutritional status of the patients did not change. The most common side effects were abdominal pain (34%), catheter sepsis (28%), and weight loss (25%).

STEPS-3: STEPS-3 (nct01560403) was a 1-year open-ended extended study that further monitored the long-term efficacy and safety of TED in treating SBS.[22] The subjects were patients with SBS who completed the STEPS and STEPS-2 studies. At the end of STEPS-3, patients who received TED in STEPS, STEPS-2, and STEPS-3 had received TED for 43 months (group 1), and patients who received TED in STEPS-2 and STEPS-3 had received TED for 36 months (group 2). Fourteen patients were enrolled, and 13 completed the study. The results illustrated that compared with the

baseline level, the average PS volume had decreased by 9.8 L/week in group 1 (vs. 3.9 L/week in group 2), and the PN frequency had decreased by 3.0 days/week in group 1 (vs. 2.1 days/week in group 2). Two patients ended PN after 126 and 130 weeks of TED treatment, respectively. The other two patients who ended PN in the STEPS-2 study remained intestinal self-sustaining in the STEPS-3 study. In general, TED can reduce or end PN dependence and help patients achieve intestinal self-sustainment. The long-term efficacy of TED is sustained and stable, but the duration of TED treatment remains difficult to determine.

Cost. According to NPS Pharmaceuticals, the development cost of the Gattex project was $250 million. On 12 January 2013, NPS Pharmaceuticals announced that the annual cost of Gattex per patient with SPS was $295,000, and the company estimated that as few as 3000 patients who had SBS with intestinal failure would be available for treatment in the United States. According to NPS Pharmaceuticals, approximately half of United States-based patients would be on commercial insurance. Another third would be on Medicare, and the rest would receive Gattex for free.[23] In some European countries, Revestive (commercial name of TED outside the United States) has been used clinically at a similar price.[24,25]

SBS population characteristics with significant therapeutic effects of TED. Because of differences in etiology, residual intestinal anatomy, and PS dependence, the therapeutic effects of TED differ among individual patients with SBS. In view of the high cost of TED treatment, it is of great clinical value to identify predictive factors of TED efficacy. Jeppesen *et al.*[26] summarized the clinical characteristics of patients with SBS who were able to significantly reduce PN after using TED in the STEPS study and found that higher baseline values of PS were associated with more significant decreases of PS. Chen *et al.*[27] found that patients with SBS caused by Crohn's disease, loss of the terminal ileum or ileocecal valve, colon discontinuity, or less residual colon experienced stronger therapeutic effects of TED treatment.

Duration of administration. When Schwartz *et al.*[21] discussed the duration of TED in the STEPS-2 study, they found that the volume of PN reduction was proportional to the duration of TED administration. However, the timing of PN decreases does not completely coincide with the timing of TED treatment. Some patients required prolonged treatment before PN decreased, and the specific time was difficult to determine. After the STEPS-2 study, the diminution of PN was still >20% in patients with SBS who experienced good TED efficacy. Seven of the eight patients who did not respond to TED in the STEPS study displayed a decrease of PN in STEPS-2. Patients with a delayed response to TED had a PN duration of 1.1 to 9.8 years, colon in continuity, and a residual small bowel of 30 to 120 cm. After 24 to 104 weeks of TED treatment, the average demand for PN decreased from 3.5 to 26.6 L/week (baseline) to 3.1 to 16.6 L/week, and three patients ended PN. Seidner *et al.*[28] analyzed the STEPS series of studies and found that the duration of TED treatment in patients with SBS who exhibited good responses to TED was more than 6 months. In conclusion, the efficacy of TED is related to the duration of treatment. Most patients reduced their dependence on PN, and the patients with the largest decrease in PN belonged to the subgroup with the longest duration of TED treatment.

Drug withdrawal. The main clinical manifestations are observed after drug withdrawal

are decreased food intake, increased PN volume, increased wet weight of stool and urine volume, and decreased body mass index (BMI) in some patients.

Jeppesen *et al.*[29] evaluated 11 patients (nine patients with type I SBS) who had been treated with TED for 2 consecutive years for 8 weeks and found that during the washout period, oral food intake decreased without returning to the baseline level. Fecal wet weight and urine volume (which decreased during GLP-2 treatment) increased to their baseline levels but returned to the original levels after 13 weeks of GLP-2 treatment.

Compher *et al.*[30] followed up patients in the TED phase III study (nct00081458). They assessed changes in PN volume and BMI after 12 months of discontinuation in patients who had used TED for at least 24 weeks (n = 37) and who responded well to TED during the study (decrease in weekly PN volume by >20% from baseline; n = 25).[30] They found that the PN volume and BMI of patients with SBS both increased.

Potential side effects and risks. According to existing studies, the side effects of TED are stomal nipple enlargement, mild leg edema, nausea, vomiting, abdominal pain, diarrhea, fatigue, weight loss, gastrointestinal polyps, and increased growth of existing tumors. For example, in the STEPS-2 study,[21] 52% of patients (46/88) had adverse reactions related to TED, most of which were mild or moderate, and abdominal pain had the highest incidence among all adverse events (n = 30, 34%). In the STEPS-2 study, 18% (9/50) of patients (n = 3, TED/TED; n = 6, placebo/TED) developed gastrointestinal polyps; among these patients, two had polyps before treatment. Specifically, the polyps were adenomas (n = 5), hyperplastic polyps (n = 1), inflammatory polyps (n = 1), and unclassified polyps (n = 2). The detection rate of polyps (18%, 9/51) was within the expected detection range of adenoma (greater than 15%/25% for women/men aged ≥50 years). In an analysis of the STEPS series, Armstrong also found that TED can induce colonic polyp formation.[31] Armstrong determined that the rates of colonic polyps were 12% and 18% before and after TED treatment, respectively, and the pathologies were all benign. Other studies indicated that 30 months of TED treatment does not increase the risk of intestinal cancer in tumor-free animals or patients, but it may promote the growth of existing tumors.[32] Therefore, tumors must be removed before TED treatment.

Quality of life. Baxter *et al.*[33] assessed the relationship between quality of life and the days of PN per week. Their study included 699 patients from 14 countries and revealed that the life quality score was negatively correlated with the duration of PS and weekly usage times. Patients with SBS caused by Crohn's disease and mesenteric ischemia had higher scores, whereas patients living alone had lower scores. Another recent multicenter study confirmed that the frequency of PN use per week was negatively correlated with quality of life.[34]

Periodic monitoring. In Europe and the United States, the internal milieu should be closely monitored before and during treatment to avoid fluid imbalances and electrolyte disturbances.[22,35] Total colonoscopy should be performed before and 1 year after treatment. Polyps should be removed. The frequency of colonoscopy should be based on the monitoring guidelines after polypectomy (at least once every 5 years).[36]

TED adjustment for patients with SBS approaching intestinal autonomy. No relevant evidence regarding the adjustment of TED administration for patients with SBS approaching intestinal autonomy has been

established to date. However, the intake of nutrients, water, electrolytes, and trace elements should be closely monitored in such patients. TED can promote the intestinal absorption of nutrients, including water, which can easily lead to excessive water retention in the body. Therefore, the dose of TED needs to be adjusted in a timely manner when patients have hyperdynamic circulation.[37]

Strategy of GLP-2 analogs: recommended dose and contraindications. In Europe, TED is used in adults and children older than 1 year with stable postoperative intestinal absorption function.[38] The conventionally recommended dose for all patients is 0.05 mg/kg once a day subcutaneously injected into the abdomen or thigh. The therapeutic effect should be evaluated after 6 months in adults and after 12 weeks in children. If there is no effect, treatment should be stopped. If the patient has a good response to TED, continuation of treatment is recommended. The latest view is that TED treatment should be continued in patients who are able to be weaned off PN.[39] Patients with SBS who have suspected or advanced malignant tumors or a history of digestive tract (including biliary tract) malignant tumors within 5 years are contraindicated for TED treatment.

GLE

GLE is a peptide that contains nine amino acid substitutions and six lysine residues at the end of the C-terminus. It is a new GLP-2 analog with a half-life of 50 hours, and it is administered as a subcutaneous injection once or twice weekly. The application of GLE in patients with SBS is still in the clinical research stage. In 2019, Naimi *et al.*[40] explored the potential therapeutic effects of three different GLE doses in patients with SBS. The study was a single-center, double-blind, crossover, randomized phase II trial. Eighteen patients with SBS who had a stool volume of >1500 g/day were randomly divided into six groups. Each group received two GLE doses. Each dose was given for 3 weeks with a washout period of 4 to 8 weeks. The doses in the six groups were set as follows: 10 mg/1 mg, 10 mg/0.1 mg, 1 mg/10 mg, 1 mg/0.1 mg, 0.1 mg/10 mg, and 0.1 mg/1 mg. The results illustrated that GLE was well tolerated in patients with SBS. The fecal volume was significantly reduced in the 1 and 10 mg groups, but not in the 0.1 mg group. The side effects included stoma complications (72%), injection site reactions (61%), peripheral edema (56%), nausea and abdominal pain (44%), polyuria and fatigue (33%), abdominal distension (28%), vomiting and dizziness (28%), cough (22%), and anorexia (22%). In 2020, further research demonstrated that GLE can increase the intestinal transit time and promote intestinal mucosal growth and absorption.[41] A phase III clinical trial examining the effect of GLE on SBS started in October 2018, and it remains in progress.

APRA

APRA, a novel long-acting selective GLP-2 analog, differs from both native GLP-2 and TED mainly by three amino acid changes.[42] It has the same selectivity and potency as natural hGLP-2 in relation to the GLP-2 receptor, but it has a lower clearance rate, longer half-life, and higher plasma protein binding rate. In rat intravenous pharmacokinetic studies, the clearance rates of hGLP-2, TED, GLE, and APRA were 25, 9.9, 2.4, and 0.27 mL/kg/min, respectively, with half-lives of 6.4, 19, 18, and 159 minutes, respectively. The terminal half-life of APRA following subcutaneous administration in humans and various animal species is approximately 30 hours, allowing the possibility for only once- to twice-weekly treatment. In 2020, Martchenko *et al.*[43] found that after 3 weeks of APRA

treatment, the depth of small intestinal crypts and villus heights of mice were significantly increased ($P < 0.001$), and the number and circumference of small intestinal glands increased after 7 and 10 weeks ($P < 0.01$); however, the colon remained unchanged. This result is consistent with that reported by Slim *et al.*[44] In the same year, Pauline *et al.*[45] compared the effects of TED and APRA in an SBS pig model. The four groups in their study were the saline group (control; n = 8), APRA group (APRA/BIW, 5 mg/kg twice a week; n = 8), TED group 1 (TED/QD, 0.05 mg/kg four times a day; n = 8), and TED group 2 (TED/BID, 0.05 mg/kg twice a day; n = 7).[45] Compared with the findings in TED group 1, APRA had a better nourishing effect on the intestinal mucosa. APRA also had some clinical benefits versus the observations in TED group 2. From a clinical viewpoint, improvement of the pharmacokinetic characteristics of APRA will provide more considerable benefits for the treatment of SBS. Therefore, APRA was designated an orphan drug by the United States Food and Drug Administration for the treatment of SBS in 2019.

GLP-2 analog treatment strategy

Given the high cost and high risks of rejection and infection after small bowel transplantation, intestinal rehabilitation is the first choice for patients with SBS. GLP-2 analogs represent the first successful pharmacological intervention that safely and effectively augments the natural process of adaptation and provides a clinical benefit in terms of a reduction in PN volume in patients with SBS.[46,47] Its long-term side effects are unknown, and they can only be observed through long-term follow-up. TED is recommended for adults and >1-year-old children with SBS under the condition that the benefits and the known and unknown risks of TED are conveyed to patients. GLE and APRA remain in clinical development.

Conclusion

GLP-2 analogs are the first batch of candidate drugs for nutritional intestinal hormone therapy, representing a new frontier of treatment for SBS. Because of their ability to increase intestinal absorption, diminish fecal losses, eliminate or reduce the need for PN, and reduce the time spent on PN, GLP-2 analogs are playing an increasingly important role in intestinal rehabilitation and improvement of quality of life. They may become preferred medications for patients with SBS in the future. Further research is needed to verify the safety and long-term side effects of GLP-2 analogs. Their high cost may limit their clinical application to a certain extent.

Author contributions

Yuanxin Li provided design assistance and guidance. Changzhen Zhu consulted the literature and completed the writing.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and publication of this article: This review was supported by the Initial Scientific Research Fund of Young of Beijing Tsinghua Changgung Hospital (No. 12020C1003).

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