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Short Bowel Syndrome in Adults – Part 5

Trophic Agents in the Treatment of Short Bowel Syndrome

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An important goal when treating the short bowel syndrome (SBS) patient who requires parenteral nutrition or fluid support is to reduce dependency on this support and, whenever possible, to eliminate its use altogether. There is great interest in the use of growth factors in patients with SBS who have been unable to achieve enteral independence during the adaptive period despite optimization of diet and medical management. A number of pharmacological agents have been demonstrated to induce trophic properties on the intestinal epithelium. In Part V, the final part of this series on SBS, we will focus on somatropin, a recombinant human growth hormone, and teduglutide, a recombinant human glucagon-like peptide-2 analogue, the currently approved trophic factors available for use as aids to wean parenteral support in SBS.

INTRODUCTION

An otherwise healthy 45 year-old man underwent laparoscopic cholecystectomy for acute cholecystitis. His postoperative course was complicated by an undetected vascular injury causing widespread bowel necrosis requiring extensive resection leaving him with about 90 cm of jejunum anastomosed to his transverse colon. He has been on home parenteral nutrition (PN) since September 2011. Previous attempts to wean him from the PN have stalled at 4 nights per week despite adherence to aggressive dietary and pharmacologic strategies. Although he has experienced no complications from the PN, and is otherwise doing well, he desires to be off PN due to its untoward effects on his quality of life.

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Are there any other non-surgical treatment options that may allow him to further wean and potentially eliminate his need for PN?

While life saving, PN use in short bowel syndrome (SBS) is associated with a reduction in quality of life and a number of complications arising from not only the PN, but also the catheter used to infuse the PN. These complications may include catheter-related bloodstream infections and venous thrombosis, metabolic bone disease, liver disease, and renal failure (See Part I in this series). An important goal when treating the SBS patient who requires parenteral support (i.e., PN or intravenous fluids [IVF]) is to reduce dependency on this support and, whenever possible, eliminate its use altogether. PN requirements decrease as the bowel

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adapts following resection allowing greater nutrient and fluid absorption. Over 50% of adults with SBS can be weaned completely from PN within 5 years of diagnosis.[1,2] In contrast, the probability of eliminating PN use is < 6% if not successfully accomplished in the first 2 years following the individual's last bowel resection.[1] A number of clinical factors may serve as useful predictors of the success of eliminating the use of PN in SBS (Table 1). The presence of a colon and the remaining length of functional small bowel are the most critical factors. Permanent need of PN generally occurs when there is < 50-70 cm of small bowel with colon-in-continuity or < 100-150 cm of small bowel when the colon is absent.[1]

Following the 2 – 3 year period of greatest intestinal adaptation after massive resection, a homeostatic/maintenance stage begins where no further spontaneous intestinal adaptation is thought to occur. Intestinal failure is frequently considered permanent when PN is required beyond this stage. There is great interest in the use of growth factors in patients with SBS who have been unable to achieve enteral independence during the adaptive period despite optimization of diet and medical management. The current understanding of the adaptation process has led to the study of hormones, nutrients, and growth factors in experimental models and in humans with SBS. A number of pharmacological agents have been demonstrated to induce trophic properties on the intestinal epithelium in animal models of SBS. These encouraging reports have been followed by conflicting reports of efficacy in humans regarding the enhancement of intestinal absorption, adaptive changes to the gut and utility in PN weaning. This review will focus on *somatropin* (Zorbtive™; Serono Inc., Rockland, MA), a recombinant human growth hormone, and *teduglutide* (Gattex®; NPS Pharmaceuticals, Bedminster, NJ), a recombinant human glucagon-like peptide-2 analogue, as they are both Food and Drug Administration (FDA)-approved for use as aids to wean parenteral support in SBS patients.

Growth Hormone

Growth hormone (GH) has been shown to promote crypt cell proliferation, mucosal growth, collagen deposition, and mesenchymal cell proliferation via insulin-like growth factor-1 and suppressor of cytokine signaling-2. Enhanced intestinal absorption has repeatedly been demonstrated in animal models of SBS, while there have been conflicting reports in humans. In 1995, Byrne et al. reported on 47 patients, most of whom had a colon-in-continuity, treated with a combination of growth hormone (GH), oral glutamine and an optimized SBS diet for 3 weeks in a controlled inpatient-like setting followed by continued use of the diet and glutamine.[3] With follow-up for as long as 5 years, they showed that 40% of patients could be weaned completely from PN while another 50% could make significant reductions in their PN use.[4] With these reports, the concept of *intestinal rehabilitation* was introduced.[5,6] In a more recent uncontrolled, prospective case series, Zhu and colleagues used a similar treatment program and demonstrated very similar, long-lasting results.[7]

Table 1. Clinical Factors Influencing Successful Weaning from Parenteral Nutrition

- Provision of intact luminal nutrients
- Length of the remaining functional small intestine
- Presence of a colon
- Presence of an ileum/ileocecal valve
- Absence of mucosal disease in the remnant bowel
- Degree to which intestinal adaptation has occurred
- Appropriate selection and use of antimotility and antisecretory agents
- Patient age
- Duration of time on parenteral nutrition
- Nutritional status prior to attempted parenteral nutrition weaning

A phase III prospective, randomized, placebo-controlled trial conducted at 2 centers was subsequently performed. Forty-one PN-dependent SBS patients (most with colon-in-continuity) were enrolled and studied in an inpatient-like setting for 6 weeks; 2 weeks of diet and medication (i.e., antidiarrheal and proton pump inhibitor) optimization and PN stabilization followed by a 4-week treatment period. Patients were randomized into 3 groups: somatropin (0.10 mg/kg subcutaneously once daily) with glutamine, somatropin without glutamine, and placebo with glutamine. A significant reduction was seen in both groups treated with GH in PN requirements (the primary endpoint), including PN

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volume, PN energy and frequency of PN infusions at the end of the 4-week treatment period (Table 2). The extent of reduction, however, was greatest in the group receiving somatropin in combination with glutamine.[8] PN reduction remained significantly reduced during a 12-week observation period in the somatropin with glutamine group only; importantly, a weight loss of about 5 kg was also observed in this group. Although tolerated, peripheral edema and musculoskeletal complaints were common in the somatropin treated groups. On the basis of this evidence, and the safety of the treatment program, the FDA approved the use of somatropin in December 2003 as a short-term (4 weeks) aid for PN weaning in patients with SBS. To date, somatropin has not been approved by the European Medicines Agency for this indication.

Despite the reports of success with GH, 3 randomized, controlled nutrient balance studies found conflicting evidence with respect to nutrient and wet weight absorption[9-11] using this combination of somatropin and glutamine (but without diet or conventional medication optimization). This has led to a considerable amount of skepticism surrounding the long-term benefits of this approach and its clinical use remains controversial.[12] Additionally, side effects of somatropin including peripheral edema, arthralgias and carpal tunnel syndrome are significant, further limiting its adoption into clinical practice. Concern exists about a potential increased risk of colorectal cancer in patients receiving somatropin if required to be administered over a longer period of time.[13] Finally, there is also concern about the feasibility of replicating the results of the pivotal trial in an ambulatory setting without the same daily monitoring and counseling provided. Clearly, admitting a patient for 4 weeks to optimize diet, hydration and medical therapy and administer somatropin would be rather challenging in the present healthcare environment.

Contraindications, Precautions and Costs Associated with Somatropin Use

Somatropin is contraindicated in patients with active neoplasia and in those who are acutely critically ill. It has been associated with acute pancreatitis, impaired glucose tolerance, type 2 diabetes mellitus, carpal tunnel syndrome and arthralgias. In the U.S., the cost of a 4-week course of somatropin is approximately $20,000.[28] An economic analysis of healthcare costs associated with GH use estimated a 2-year savings of $85,474 assuming that 34% of GH-treated patients eliminated PN use within 6 weeks of treatment and 31% remained PN-free after 2 years.[29] However, remember that patients in the clinical trial were studied in an inpatient setting (albeit not hospital), and received daily visits and education/counseling; costs not factored into the dollar amount mentioned above. How the use of this agent will translate into the ambulatory setting where visits and supervision will not be as intensive is unknown. It has not been widely adopted into clinical practice more than a decade after its approval. Furthermore, the role of repeated course(s) or prolonged treatment with somatropin requires additional study.

Glucagon-like Peptide-2

Glucagon-like peptide-2 (GLP-2), secreted from distal small intestine and proximal colonic mucosal L-cells in response to luminal nutrients, plays an important role in intestinal adaptation. GLP-2 administration induces epithelial proliferation in the stomach, small bowel and colon by stimulating crypt cell proliferation and inhibiting enterocyte apoptosis, increases absorptive capacity and inhibits gut motility and secretion.[14-18] In a small, open-label trial investigating the effects of GLP-2 in humans with SBS, 8 patients received 400 μg GLP-2 subcutaneously twice daily for 35 days.[19] Of the 8 patients studied, 4 had a portion of colon-in-continuity and were receiving PN while the other 4 did not have a colon and did not require PN. An increase in overall energy absorption, decrease in fecal wet weight, slowing of gastric emptying and nonsignificant trend toward increased jejunal villus height and crypt depth were demonstrated.

Teduglutide, a recombinant, degradation-resistant, longer acting GLP-2 analogue, was shown in an open-label study to be safe, well-tolerated, intestinotrophic and significantly increased intestinal wet weight absorption, but not energy absorption in 16 SBS patients with an end-jejunostomy or a colon-in-continuity.[20] Teduglutide was then studied in two phase III multinational, randomized, double-blind, placebo-controlled trials that included a total of 169 PN or parenteral fluid-requiring SBS patients in an outpatient setting (Table 2). A habitual diet was followed by patients in both trials. Notably, only about one-half of the subjects used antidiarrheal and antisecretory medications during the studies. In the first study, 83 SBS patients were separated into 3 treatment arms (placebo, 0.05 mg/kg/d and 0.10 mg/kg/d

Table 2. Summary of Published Phase III Clinical Trials and Extension Studies of Somatropin and Teduglutide in SBS

	Somatropin[8]			Teduglutide[21]			Teduglutide[25]	
Study Group	a) PBO+ Gln	b) GH-Gln	c) GH+Gln	a) PBO	b) TED 0.05	c) TED 0.10	a) PBO	b) TED 0.05
Diet	HCLF	HCLF	HCLF	Habitual	Habitual	Habitual	Habitual	Habitual
Glutamine	30 g PO	None	30 g PO	-	-	-	-	-
Subjects (#)	9	16	16	16	35	32	43	43
Remnant SB Length (cm)	62±31	84±50	68±33	77±23	58±44	68±43	69±64	84±65
Colon Present	8	15	13	11	26	19	23	26
Study Drug	None	GH 0.1 mg/kg/d	GH 0.1 mg/kg/d	None	TED 0.05 mg/kg/d	TED 0.1 mg/kg/d	None	TED 0.05 mg/kg/d
Duration	**4 wks**	**4 wks**	**4 wks**	**24 wks**	**24 wks**	**24 wks**	**24 wks**	**24 wks**
Δ PN Volume, L/wk	-3.8	-5.9*a vs. b	-7.7† a vs. c	-0.9	-2.5	-2.5	-2.3	-4.4† a vs. b
Δ PN Energy, kcal/wk	-2633	-4388*a vs. b	-5751† a vs. c	-406	-1526	-749	NR	NR
>20% Decrease in PN	-	-	-	6%	46%‡a vs. b	25%	30%	63%**a vs. b
Δ Body Weight, kg	-0.6	1.2	1.8	0.2	1.2	1.4	-0.6	1.0
Duration	**16 wks (OBS only)**	**16 wks (OBS only)**	**16 wks (OBS only)**	**-**	**52 wks (Treatment) (N=19/25)**	**52 wks (Treatment) (N=23/27)**	**-**	**-**
Δ PN Volume, L/wk	-4.7	NR	-7.2*a vs. c	-	-4.9	-3.3	-	-
Δ PN energy, kcal/wk	NR	NR	NR*a vs. c	-	-3511	-1556	-	-
>20% Decrease in PN	-	-	-	-	68%	52%	-	-
Δ Body Weight, kg	-2.5	-4.0	-5.2	-	NR	NR	-	-

PBO (placebo); GH (growth hormone); TED (teduglutide); HCLF (high carbohydrate, low fat); OBS (observation); NR (not reported)
***P<0.05; †P< 0.001; ‡P=0.005; **P=0.002**

administered subcutaneously once daily) and treated with the study medication for 6 months following a PN optimization period. PN weaning was the primary endpoint (20% reduction by week 20 and maintained to week 24). Teduglutide was found to be safe and well tolerated; however, only the lower teduglutide dose significantly reduced PN requirements (46% for 0.05 mg/kg/d versus 6% for placebo), and 3 patients were completely weaned from PN.[21] There was a strong trend towards overall reduction in fluid volume at the end of treatment in the teduglutide treated groups compared to placebo (2.5 L/wk vs. 0.9 L/wk, respectively; *P*=0.08). Parenteral energy intake, while much lower than baseline, was not significantly different from placebo at the end of 24 weeks of treatment (*P*=0.11). Villus height, plasma citrulline concentration and lean body mass were significantly increased in the teduglutide groups compared to placebo; no evidence of dysplasia in the intestinal samples was detected.[22] After stopping teduglutide at the end of the 24 week treatment period, some patients (15/37) required an immediate increase in their fluids while others (22/37) seemed to maintain their fluid requirements and body weight.[23] Indicators of sustained fluid reduction and maintenance of body weight included a longer length of the remaining small bowel and the presence of at least a portion of colon, lower body mass index at baseline, and lower PN volume reduction while on teduglutide (i.e., they were already receiving lower volume of parenteral support at baseline).

During long-term (an additional 28 weeks) treatment of 52 patients from the original 24-week study, at week 52, 68% of the 0.05-mg/kg/d and 52% of the 0.10-mg/kg/d dose group had a ≥ 20% reduction in PN, with a reduction of 1 or more days of PN dependency in 68% and 37%, respectively.[24] Those treated with the lower dose showed continued decrease in parenteral volume requirements (4.9 L/wk); 4 patients achieved complete independence from PN. Overall, it appears that long-term treatment is associated with continued improvement.

The second trial compared the lower dose of

Table 3. When to Consider the Use of a Trophic Agent

- PN/IV fluids > 3 times per week for >1 year
  - Possible exceptions include:
    - < 1 year on PN/IV fluids, with > 1 septic episodes
    - Patient miserable, stool output unbearable with conventional agents maximized
- Clinically stable and well nourished
- Optimized short bowel diet and hydration therapy (See Parts II and III of this series on SBS for details)
- Motivated patient with a desire to reduce or discontinue the parenteral support
- All efforts at medication intervention have been maximized including dose, form, frequency, agent (See Parts IVA & IVB of this series on SBS for details):
  - Anti-secretory agents
    - Proton pump inhibitors
    - Octreotide (rarely, when appropriate)
  - Anti-diarrheal agents
    - loperamide, diphenoxylate, and if ineffective → narcotics
- Absence of GI anatomical contraindication (stricture, obstruction/narrowing, active Crohn's disease, etc.)
- No contraindications for trophic agent use
  - Active GI neoplasia
  - Active non-GI malignancy—assess risk vs. benefit
- Patient has demonstrated compliance/reliability with other therapies
- Partnership exists between treatment team and patient

teduglutide to placebo administered for 6 months in 86 adult SBS patients and utilized a more aggressive PN weaning strategy (10-30% vs. 10% reductions at 2-weekly intervals and starting at week 2 vs. week 4.[24] Once again, a significant benefit of teduglutide over placebo was seen (Table 2). Those receiving teduglutide were more than twice as likely to respond to therapy (63% versus 30%, P=0.02). The mean reduction in PN volume after 24 weeks was 4.4 L in the teduglutide group compared to 2.3 L in the placebo group. Fifty-four percent of those receiving teduglutide reduced at least 1 PN infusion day/week compared with 23% for placebo. No subjects were completely weaned from PN at the end of 24 weeks of treatment. In a preliminary report from a 2-year extension study, 65 patients (74%) completed the study. Of the 30 patients treated for 30 months with teduglutide, 28 (93%) made significant reductions in their parenteral support with a mean decrease of 7.6 L/wk, and 21 (70%) eliminated at least 1 infusion day.[26] A total of 15 of the 134 (11%) patients treated in both phase III studies and their extension studies achieved enteral autonomy.[27] Most of these patients had a portion of colon-in-continuity and lower baseline PN/IVF requirements. Due to the small numbers, a formal statistical analysis for predictive factors was not possible.

The most frequent gastrointestinal side effects reported in both trials included abdominal pain, nausea, stomal changes (in those with an ostomy), abdominal distension and peripheral edema; resolution occurred with treatment continuation or temporary discontinuation in most instances. Data from the extension studies suggest a tolerable safety profile with abdominal pain, injection site reactions and stomal complaints being most common (24). Although anti-teduglutide antibodies have been demonstrated in the blood of treated patients, they appear to be non-neutralizing and have not been shown to decrease the effect on PN volume reduction (25). Thus, it appears that long-term teduglutide treatment is associated with acceptable tolerability and continued improvement. On the basis of the data from these two pivotal trials, teduglutide was approved by the United States FDA in December 2012 and by the European Medicines Agency in 2012 (Revestive®; Nycomed, Zurich, Switzerland) for SBS patients as a long-term aid to PN weaning.

Contraindications, Precautions and Costs Associated with Teduglutide Use

The only contraindication to teduglutide use is active GI neoplasia. In patients with active, non-GI neoplasia,

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use should only be considered if benefits outweigh the risks. Precaution is necessary, however, due to a number of potential adverse effects including increased fluid absorption and the potential for fluid overload; the potential to increase drug absorption requiring dosage reduction and drug monitoring when using medications with narrow therapeutic window or require titration (e.g., benzodiazepines, opioids, psychotropics), and the risk for acceleration of neoplastic growth within the gut requiring periodic colonoscopic surveillance before and during its use (6 months before, 1 year after, and at least every 5 years thereafter). Additional monitoring for gastrointestinal obstruction, gallbladder, biliary and pancreatic disease (amylase, lipase, alkaline phosphatase and total bilirubin before and every 6 months while using) is also advised as part of the risk evaluation and mitigation strategy (REMS- https://www.gattex.com/hcp/rems.aspx) program required of prescribers (see Table 4 for one institution's monitoring form). Given the average annual cost of $295,000 associated with teduglutide use in the U.S., appropriate patient selection will be important to determine the proper place for this therapy in the management of the PN-requiring SBS patient. Of note, in the U.S., the cost to the individual is generally much lower as a result of insurance coverage and patient support programs that provide financial assistance for out-of-pocket expenses. One other interesting predicament that may need to be considered, particularly in those patients weaned entirely from PN support while using teduglutide, is that there may be a potential for insurance denial of coverage of continued use of teduglutide since the patient is no longer using PN; letter writing and/or phone calls to the insurance company may be needed in this situation. It is important to recognize that the reduction in costs associated with PN use as weaning progresses will offset some of the cost associated with the use of teduglutide. Finally, some clinically important outcomes that defy accounting may come in the form of a dramatically improved quality of life as a result of decreased stool output, preserved hepatic function due to less PN dependence, and even an intestinal transplant avoided. Although these outcomes are difficult to quantify, to SBS patients and the clinicians who care for them, they are worthy goals.

Practical Approach to PN Weaning

The eligibility criteria used in the phase III clinical trials only provide a guide to aid in determining which patients should be considered for trophic factor use. At present, these agents should not be used in the pediatric population outside of the setting of a clinical research study. Suitable patients include those with SBS who have neither obstructive nor active GI malignant disease and who are dependent upon PN or IVF support despite optimization of diet, oral fluids and adjunctive medications (See Part II, III, IV A & B of this series). They should also be nutritionally optimized and in fluid balance. Furthermore, the patient should be motivated with a desire to reduce or discontinue the parenteral support. The presence/absence of a colon and length of the remaining small bowel do not necessarily factor into the selection of appropriate candidates and virtually any bowel anatomies can be considered. Table 3 lists factors to consider when determining whether to enlist a trophic factor in the care of the patient with SBS.

Prior to weaning, regardless of the use of a trophic factor, it is important for the SBS patient to recognize that the 'trade-off' to not being on PN is the need to take several medications orally and increase the amount of food and fluid ingested daily. Major lifestyle changes and increased out-of-pocket expenses are generally required. Consequently, patient education regarding the care plan (e.g., diet and drugs to be used and PN weaning plan) and ongoing support is important to enhance compliance. This is best done in the setting of a multidisciplinary practice with healthcare providers experienced in the care of SBS patients.

Before PN weaning begins, as previously mentioned but important to reemphasize, the SBS patient's diet, fluid intake and conventional antidiarrheal and antisecretory medications should be optimized. Additionally, certain criteria should be met before reducing PN that include meeting the daily calorie and fluid intake goals established for the patient. Frequent follow-up is necessary with subsequent PN reductions based on tolerance as determined by the development of symptoms, hydration status, electrolytes and weight.[30] A useful approach to monitor hydration status is to maintain the urinary sodium concentration > 20 mEq/L and daily urinary volume > 1 L (on PN free nights) and enteral balance (oral fluid intake minus stool output) between 500 and 1000 mL/d. Monitoring stool and urine output is cumbersome, however, SBS patients attempting to wean PN tend to be highly motivated. Providing the patient with tools to measure both stool and urine as well as a diary to record this information

Table 4. Sample of University of Virginia Health System Teduglutide Monitoring Form

Patient Name: _____

Trophic Agent Start Date: _____

GI Anatomy: _____

Current Oral Diet: _____

PN/ Fluids: _____

Date →			**Date →**				**Date →**			
Parameter ↓	Baseline	6-12 months	**Parameter ↓**				**Parameter ↓**			
Colonoscopy			Weight				Sodium			
Amylase			Stool/ostomy volume (mL)				Potassium			
Lipase			Urine output				Chloride			
Total bilirubin			Abdominal pain				HCO3			
Alk phos			Abdominal distension				BUN			
			Nausea				Creatinine			
			Peripheral edema				Magnesium			
			Gas				Phosphorus			
			Vomiting							
			Fatigue							
			Dyspnea							

Note: Frequency of monitoring should be individualized

for review and discussion at the office, via e-mail, or over the phone is helpful.[31]

Once daily subcutaneous injection is required for the use of either somatropin or teduglutide. As injection site reactions are relatively common, rotating the injection site among the abdomen, thigh and upper arm is recommended. The injection should be administered at about the same time each day. The patients should be aware of the precautions necessary with the use of these medications and be instructed on the proper monitoring for complications and what to do/whom to contact should a problem occur. There are no data on the use of these agents in the presence of octreotide, biologic agents or immunosuppressant therapies.

PN reductions can be made by either decreasing the days that PN is infused/week or by decreasing the daily PN infusion volume equally throughout the week (e.g., 10%-30% reduction).[30] Patients tend to prefer the former; however, dehydration is less of a potential concern with the latter. The teduglutide studies used the latter approach while the phase III somatropin study used the former approach. An optimal interval for making PN reduction decisions has not been defined. At most, in the ambulatory setting, once weekly would seem appropriate while acknowledging that this needs to be individualized. A recent report recommended obtaining laboratory studies weekly with an office visit monthly until parenteral requirements are stable, after which the frequency of monitoring and visits can be reduced.[31] Once PN infusions are < 3 d/week, a trial of PN discontinuation is suggested. Although the occasional patient may successfully discontinue PN

without the gradual weaning strategy, this approach is not recommended for the SBS who has been receiving PN for an extended period of time.

Oral micronutrient supplementation becomes necessary as PN is weaned and levels require periodic monitoring. Electrolyte supplementation, usually magnesium and/or potassium and sometimes bicarbonate, may also be needed and require monitoring. The frequency of monitoring will depend upon the stage of PN weaning and the presence of existing or prior deficiencies.[30] Periodic laboratory monitoring will need to continue indefinitely, even in those weaned completely from PN.

CONCLUSION

An important goal in the treatment of SBS is to improve enteral autonomy, thereby reducing and, occasionally, eliminating the need for PN or IVF support. Following optimization of diet, hydration and conventional pharmacological strategies (and occasionally surgical reconstructive procedures), the use of trophic factors has the potential to bring about further reductions. The currently available agents include somatropin, a recombinant human GH, and teduglutide, a recombinant human GLP-2 analogue. Both agents, while quite different in terms of duration of use, cost and adverse effects, have been shown in randomized, placebo-controlled trials to facilitate weaning from parenteral support. Long-term safety and efficacy, timing of administration in relation to the onset of SBS, optimal patient selection for use, duration of treatment and cost effectiveness of both somatropin and teduglutide strategies will require further study. ■

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