

Teduglutide and Short Bowel Syndrome: Every Night Without Parenteral Fluids Is a Good Night

See “Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure,” by Jeppesen PB, Pertkiewicz M, Messing B, et al, on page 1473.

Short bowel syndrome (SBS) is characterized by either a congenital or acquired absence of a substantial portion of the small intestine. Those patients whose resultant malabsorption is insufficient to maintain nutritional or fluid autonomy (eg, fecal energy and/or fluid losses are greater than absorption) are deemed to have intestinal failure (IF). Although most nutrient absorption occurs within the proximal 100–150 cm of jejunum,¹ intestinal transit time is very rapid, allowing for limited nutrient–epithelial contact time. Such individuals are among the most complex and challenging to manage patients of any gastrointestinal disease. Particularly difficult to manage are those patients with a proximal jejunostomy, who may actually secrete more fluid than they ingest.² Adult patients typically have <200 cm of residual small bowel, with or without their colon, although absorption is dependent not only on the length of bowel, but the overall surface area and function. Underlying etiologies may include multiple small bowel resections for diseased or obstructed bowel including Crohn’s disease, trauma, mesenteric vascular catastrophes, or volvulus. Etiologies in children may also include congenital disorders such as intestinal atresia, malrotation, and gastroschisis. In part, because the underlying diseases resulting in SBS are a heterogeneous group, there is no ICD-9 code and, as such, there are no reliable estimates as to the number of individuals with SBS or SBS/IF in the United States. Estimates based on European registries and other databases have suggested the number of such patients in the United States may be in the 10,000–20,000 range.³

Patients with SBS/IF depend on artificial nutrition and/or fluid support to maintain life. This may require them to infuse parenteral fluids (parenteral support [PS]) overnight for 3–7 days per week, and in some cases, during the day as well. This therapy has substantial implications for employment, activities, sleep, and finances. Furthermore, medical management may differ depending on whether a given patient has residual colon in continuity with the remaining small intestine or not.

Numerous complications from SBS or its therapy may develop. Most notorious among these is IF-associated liver disease.⁴ IF-associated liver disease is the leading

tion, a procedure that may be life-saving and eliminate dependence on parenteral fluids, but may cost upwards of \$1 million, although often \$250,000–\$500,000 for the procedure and initial hospitalization in addition to medications, follow-up clinical visits, and treatment of complications such as infections or acute and chronic rejection and additional surgery. One year of parenteral nutrition (PN), discounting treatment for laboratory studies, nursing and physician visits, and treatment of complications and hospitalizations (generally 1–2 times annually), often costs the health care system \$100,000–\$125,000.⁵

Animal models suggest that, after massive intestinal resection, the intestine begins to adapt, whereby the intestine lengthens a modest amount, but may increase in diameter and surface area significantly. This process is more pronounced in the ileum after a jejunal resection wherein villi lengthen and crypts deepen.^{6–8} These findings are supported by limited human data,^{9–12} wherein diarrhea decreases over time after onset of SBS.¹⁰ In fact, conventional management¹³ of these patients, perhaps not always widely practiced owing to its relative complexity and unfamiliarity among clinicians,¹⁴ combined with the patient’s own innate ability for adaptation, can lead to elimination of PN in 50% of patients within 6 months of their resection.¹⁵

Growth hormone was the first medication approved by the US Food and Drug Administration (in 2003) specifically for use in patients with SBS receiving specialized nutritional support “in conjunction with optimal management”¹³ based on a 2-center controlled trial, although there was no placebo group and subjects received additional interventions in addition to growth hormone. Inconsistent results have been reported in previous clinical trials. Nevertheless, PN requirements could be reduced by approximately 2 L or 1 night weekly.¹⁶ The use of this growth factor has been limited, largely owing to concerns with regard to efficacy and the fact that only short-term use was approved. The effects of growth hormone on human intestinal absorption are unknown, although it enhances reabsorption of sodium in the distal nephron.¹⁷ Notably, patients with acromegaly have a heightened risk for development of colonic adenomas in humans, although malignancy has not been reported.¹⁸

A myriad of other growth factors may be involved in the process of postresection intestinal adaptation, including hepatocyte growth factor, vascular endothelial growth factor, cholecystokinin, transforming growth factor, epidermal growth factor, gastrin, insulin, insulin-like growth

and glucagon-like peptide-2 (GLP-2).¹⁹ GLP-2's own actions may be modulated by some of these peptides, including transforming growth factor- β , insulin-like growth factor-1, and KGF.²⁰⁻²² Each of these extracellular growth factors have the potential for human use. Epidermal growth factor is no longer commercially manufactured and KGF is used only for the treatment of mucositis currently. GLP-2 is among the first of these peptides evaluated in humans with SBS/IF.

GLP-2 is released from L cells in the distal small bowel and colon in response to food ingestion, but its release is severely blunted in patients with SBS/IF and ileal resection,²³ although meal-stimulated release is enhanced in patients with a preserved colon.²⁴ It promotes intestinal epithelial growth via increased cellular proliferation through activation of the Wnt signaling pathway, which leads to nuclear translocation of β -catenin,²⁵ and decreased apoptosis and epithelial growth may also be enhanced through increased mesenteric blood flow.²⁶

Normal digestion and absorption depends on a gradual emptying of nutrients from the stomach into the small intestine, wherein mixing with pancreatic enzymes and bile occurs. Rapid gastric emptying may result in inadequate mixing, insufficient enzymatic digestion, and impaired nutrient digestion. GLP-2 increases gastrointestinal transit time, and this may be among the mechanisms by which its use leads to decreased diarrhea.²⁷ The use of native GLP-2 has resulted in less chronic dehydration, the major factor in the development of IF-associated nephropathy in patients that require long-term PN,²⁸ among patients with SBS.²⁹ GLP-2 may also exert a beneficial effect on bone health as well,³⁰ which is adversely affected during SBS/IF.³¹ However, the actions of the native hormone are limited by rapid degradation by dipeptidylpeptidase IV, leading to a very short half-life. A long-acting analog, more resistant to this enzyme, h(Gly²)GLP-2[1-33] (teduglutide) was developed by the substitution of a glycine residue for an alanine in position 2.

In this issue of *GASTROENTEROLOGY*, Jeppesen et al³² report the results of a phase III double-blind, placebo-controlled trial of teduglutide for the purposes of enhancing nutrient and fluid absorption and weaning parenteral fluids in 86 patients with SBS/IF. This study was conceived because of discrepant results from an earlier placebo-controlled multinational study wherein a higher dose of teduglutide (0.1 mg/kg per day) seemed to be slightly less effective than the 0.05 mg/kg dose used in the current study, although a significant difference for the lower dose was not achieved when compared with placebo.³³

Jeppesen et al³² are to be congratulated for completing an extremely complex, multinational study in a very complicated group of patients, in fact the largest prospective study ever in this patient population. Patients were re-

minimum of 12 months immediately preceding the study to qualify for inclusion. This could have included PN or intravenous fluid and electrolytes alone. A strength of the study was the pretreatment PS optimization whereby individual patient fluid volumes were stabilized to achieve a urine output of 1-2 L/day over a period of 4-16 weeks before randomization. That ensured as much as possible that the baseline PS volume was required and stable, although unlike in the previous study,³³ there was no specific attempt at weaning PN before randomization.

In the current study, patients were randomized to receive teduglutide 0.05 mg/kg per day or placebo injected daily. The primary endpoint was the percentage of enrolled patients that achieved a consistent reduction in PS volume of 20%-100% from baseline at both week 20 and week 24. A 20% decrease equates to the reduction of PS from 6 to 5 nights per week, a very profound improvement for an individual patient. Given the disparity between daily fluid volumes (≥ 1.5 -8 L daily), it would have been inappropriate to have used the absolute decrease in number of days of infusion as the primary endpoint. Secondary endpoints in the study included the mean percentage and absolute volume decrease in PS and the number of patients and the time they required on study medication to be completely weaned from PS.

Attempts to wean PS were made at the discretion of individual investigators in increments of 10%-30%, beginning after 2 weeks of therapy, and then every 4 weeks for the remainder of the 24 week study. As we generally do in clinical practice, urine output was collected for 48 hours (including a night when PS were not administered if < 7 nights per week) before each study visit. This volume had to exceed the baseline value before further weaning would be considered. Discontinuing an entire day of PS was considered based on the weekly volume reduction, but the choice was left up to the investigator and patient.

There were 27 of 43 (63%) responders in the teduglutide group compared with 13 of 43 (30%) in the placebo group ($P < .02$) with differences between the group-specific responder rate at each visit. There was a nonsignificant trend toward a greater response rate in those patients with residual colon in continuity with their remaining small bowel. PS volume reduction was 4.4 ± 3.8 L per week in the teduglutide group versus 2.3 ± 2.7 L per week in the placebo group. At baseline, subjects received an average of nearly 2 L/d, so it was not surprising that no subjects were completely weaned from PS; however, the number of patients who achieved ≥ 1 full day off PS in the teduglutide group was more than double that in the placebo group (54% vs 23%; $P < .047$). PS was not completely eliminated in any patient. An earlier and more aggressive PS weaning protocol than that utilized in the

more significant decline in PS volume in the current investigations.

Consistent with an increase in intestinal mass, plasma citrulline concentration increased significantly only in the teduglutide group. Previous studies with teduglutide have shown it reduces the volume of diarrhea,³⁴ although this effect was not evaluated in the most recent investigation.³² It is to be noted that some patients with SBS/IF have sufficient nutrient absorption, but are unable to consume sufficient fluids to make up for dramatic losses, and as such require parenteral fluid and electrolytes, but not PN. Might these patients respond better to teduglutide? The data were not broken out. In addition, the effect of teduglutide on micronutrient absorption and potential independence from intravenous micronutrient supplementation was not evaluated.

Some patients failed to respond to teduglutide. Why did that occur? Because most L cells are located in the ileum and colon, patients with resection of those portions of bowel would presumably have lower native meal-stimulated serum GLP-2 concentrations and thereby might have a greater response to exogenous administration. However, there was a trend toward a greater response in patients with colon, although this difference did not attain significance. Given that nutrient absorption is a factor of not only percentage absorption, but oral intake, might teduglutide be more effective if administered postprandially rather than pre-prandially to avoid potential development of gastroparesis and early satiety? In addition, there were a substantial number of patients with Crohn's disease enrolled in the study. In a previous study, teduglutide was shown to be a potentially useful therapy for Crohn's disease, but only at a much greater dose (≥ 0.15 mg/kg per day).³⁵ Differential efficacy in patients with Crohn's disease owing to direct effects of inflammation on response to GLP-2, and therefore on mucosal repair and adaptation is, therefore, uncertain.

The placebo response was also substantially greater in the current study compared with the previous study.³³ This may have been related to a less aggressive PS weaning protocol before randomization. The current study used an "optimization" period only to stabilize urine output over a wide range (1–2 L daily). Perhaps some patients simply continue their adaptation phase much longer than others, although only 6 patients in the teduglutide group and 8 patients in the placebo group were < 2 years out (the previous study's exclusion criteria) since their last bowel resection. We are not told whether these patients responded differently to treatment.

Predictors of response to teduglutide need to be either determined or developed. Jeppesen et al³² found that the length of the residual bowel was not a factor. Perhaps one might be a baseline meal-stimulated serum GLP-2 con-

of the teduglutide or native GLP-2 studies to date despite the provision of standardized meals in an earlier study.³⁴ A study in children has identified a concentration of serum GLP-2, below which a need for PN can be predicted.³⁶ The presence of comorbid conditions that include the health of the residual bowel and perhaps underlying pathology, mesenteric blood flow, and age are likely all important cofactors.

As would be expected in the SBS/IF patient population, there were many adverse events in the study reported in this issue of *GASTROENTEROLOGY*, although these were equally distributed across teduglutide and placebo groups. Only 2 patients in the teduglutide group and 3 in the placebo group terminated the study owing to treatment-emergent adverse events (in both cases, abdominal pain that resolved within 3 days of study withdrawal in the teduglutide group). Abdominal pain and distention, nausea, peripheral edema, dyspnea, and nasopharyngitis were slightly more common in patients who received teduglutide. Stomal changes, primarily related to enlargement, were evident in a significant minority of patients in the teduglutide group as would be expected, given the hyperplastic effect of the medication on intestinal epithelial tissue as well as previous reports.^{33,34} The observation that 1 patient may have developed a transient bowel obstruction during treatment with teduglutide seems inconceivable to be related to the medication in the absence of an unrecognized pretreatment bowel obstruction given that teduglutide does not fertilize the growth of monster villi, but its use should be tempered in patients with bowel strictures, stomas with small lumens, or partial bowel obstructions.

Concern has been raised about the potential for GLP-2 to stimulate development of colonic adenomas in rodent models. The number of adenomas increased in mice treated with the chemical carcinogen 1,2 dimethylhydrazine,³⁷ although studies in different models, the APC-min/+ mouse, nude mice with colon cancer xenografts, or in GLP-2 receptor-transfected cancer cells.³⁸ A more recent investigation in azoxymethane-treated mice found development of colonic dysplasia and adenocarcinomas in animals that had been chronically treated with h(Gly²)GLP-2[1-33].³⁹ Although the risk for malignancy is hypothetical in humans, and colonoscopy is difficult in these patients, colonoscopy should be considered at baseline for those patients with residual colons and perhaps even as frequently as annually while on therapy until more long-term safety data are available. This risk must be balanced against quality-of-life improvements, and decreased complications related to enhanced absorption and, therefore, portal nutrient circulation, and decreased catheter access, which may lead to decreased infection risk. In addition to intestine and colon, GLP-2 receptors have been found in lung, the hind-

cally detectable effects have not been observed in these organs, the potential exists that chronic administration of GLP-2 could have either beneficial or detrimental effects.

Is teduglutide a “game changer?” Few treatments in SBS are. The only patients who will be able to discontinue PS completely will be those who are on the borderline between nutritional autonomy and PS dependence. Potentially, teduglutide may help some patients who sit on that “fence” from actually needing PS to begin with. What happens when teduglutide is stopped? Some preliminary evidence suggests the effects on adaptation may be persistent,⁴¹ although an earlier study noted histologic changes that trended toward baseline within 4 weeks of discontinuation.³⁵ Possibly longer treatment than that reported in this issue of *GASTROENTEROLOGY* is required.⁴² The advent of teduglutide, like most other new therapies, represents an incremental improvement in the care of patients with SBS/IF and likely will allow the clinician an additional option for patient management. Every night without PN is a good night, but whether teduglutide is a true “game changer” is not clear. Teduglutide does have the potential to improve quality of life for patients with SBS/IF, although a fully validated measure of quality of life in these patients awaits full development. I think we should look forward to the availability of teduglutide as a treatment for patients with SBS/IF and now we also eagerly await the development of longer acting analogs, as well as other growth factors such as HGF and KGF.

The future is a truly artificial, or artificially grown and harvested, intestine; even intestinal transplantation represents but a bridge at best. Although advances have been made, the practical aspects of a truly functional artificial gut—or even one constructed from a patient’s own stem cells, remains far from a clinical reality. In the meantime, teduglutide represents a significant, although incremental improvement in the treatment armamentarium for patients with SBS/IF.

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Conflicts of interest

Dr Buchman is a former consultant for NPS pharmaceuticals.

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Familial Visceral Myopathies: From Symptom-Based Syndromes to Actin-Related Diseases

See “Segregation of a missense variant in *enteric smooth muscle actin* γ -2 with autosomal dominant familial visceral myopathy,” by Lehtonen HJ, Sipponen T, Tojkander S, et al, on page 1482.

Mammals have genes that encode 6 different actin isoforms expressed in a developmental and tissue-specific fashion.¹ These actins include 2 striated muscle (skeletal and cardiac), 2 smooth muscle (vascular and visceral), and 2 non-muscle actins. Isoelectric focusing separates these actins into α - (skeletal, aortic smooth, and cardiac), β -, and γ 1- and γ 2- (cytoplasmic and enteric smooth muscle, respectively) actins. These actins share a high degree of structural homology, with no 2 actins differing in structure from one another by >5%. Furthermore, in mammalian cells, from 2 to 4 of the different actins may be simultane-

major actin found in visceral smooth muscle, and this report by Lehtonen et al² of the association of a mutation in this actin with familial visceral myopathy is significant for 2 reasons. It is the first report of a human disease associated with this particular actin isoform and it means that now mutations in each of the 6 different actin isoforms have been shown to cause human disease.^{3–7} What is particularly interesting, and it is true for the mutation focused on here, is that in a number of cases, different diseases are caused by mutations at the same site in different actins. For example, the R148S mutation in γ -smooth muscle actin causes familial visceral myopathy, whereas the mutation to C in α -smooth muscle actin causes thoracic aortic aneurysm and dissection.⁴ The R258 mutation to either H or C in α -smooth muscle actin causes thoracic aortic aneurysm and dissection,⁴ whereas in β -nonmuscle actin, an R to W mutation at the same site causes Baraitser–Winter syndrome.⁶ In a third example, a V370A mutation in γ -nonmuscle actin causes