Title: Off-label teduglutide therapy in non-intestinal failure patients with chronic malabsorption

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Abstract

**Background**: Teduglutide, a glucagon-like peptide 2 (GLP-2) analogue, has demonstrated efficacy in treating adult patients with short bowel syndrome (SBS) and dependence on parenteral nutrition (PN), but its role in chronic malabsorptive states that do not necessitate PN remains uncertain.

**Aims**: To evaluate teduglutide use beyond its approved indications and to discuss the results of this adjunctive treatment in patients resistant to established therapy.

**Results**: This series reports four patients treated with teduglutide off-label. The first case had Crohn’s Disease (CD) with persistent colocutaneous fistulae that demonstrated complete closure after eight months of teduglutide therapy. The second case involved a PN-dependent CD patient with persistent fistulae and intra-abdominal abscesses who weaned off PN and had a significant improvement in her nutritional status after three months of teduglutide therapy. The third case had CD complicated by severe malnutrition and previous PN-associated line infections, but by nine months of teduglutide therapy, she gained 5 kg and no longer required re-initiation of PN. The fourth case had a high-output diverting ileostomy with resultant impaired healing of a stage IV decubitus ulcer, and after two months of therapy, the patient’s pre-albumin increased by 250% and the ulcer had decreased by 40% in size.

**Conclusion**: The use of teduglutide might be broadened to include patients with functional SBS not meeting strict criteria for intestinal failure. Further studies should evaluate the efficacy of teduglutide in patients who may require short-term small intestine rehabilitation or who have chronically impaired absorptive capacity not yet requiring PN.

Keywords: teduglutide, short bowel syndrome, intestinal failure, parenteral nutrition, Crohn’s disease, malabsorption

**Introduction:**

Glucagon-like peptide 2 (GLP-2) is a peptide hormone that was first discovered as an intestinotrophic factor in 1996. It is produced in both the small and large bowel via enteroendocrine L-cells in response to nutritional, hormonal, and neural stimulation [1]. GLP-2 has been shown to enhance crypt cell proliferation, expand villus height, and increase nutrient absorption [1-3]. It appears to act through multiple growth factors such as IGF-1 [4] and ErbB ligands [5]. Experimental models of intestinal injury suggest GLP-2 signaling may also exert protective effects by increasing mesenteric blood flow [6], reducing intestinal inflammation [7], and facilitating structural and functional adaptation following major small bowel resection [8]. Teduglutide is a degradation-resistant analog of GLP-2 currently approved for the treatment of short bowel syndrome by the United States Food and Drug Administration (FDA) and the European Medicines Agency.

Short bowel syndrome (SBS) is a malabsorptive condition that may follow surgical resection, radiation, vascular insufficiency, or disease [9]. Teduglutide has changed the management of SBS in recent years. In a multinational, randomized, placebo-controlled phase three clinical trial, 63% of 43 patients treated with 0.05 mg/kg/day teduglutide for 24 weeks were able to achieve a 20-100% reduction in weekly PN volume at weeks 20 and 24, compared to only 30% of patients in the placebo group. These results were statistically significant [10]. More recent extension studies of up to 42 months treatment with 0.05 mg/kg/day teduglutide indicate that teduglutide treatment sustains clinically useful reductions of PN requirements in adult SBS patients [11, 12]. However, the phase three trials and their extension studies have focused primarily on adult patients with SBS and a one-year history of PN dependence but excluded those who are pregnant, with active Crohn’s disease (CD), or used immunosuppressive medications [10-14]. Furthermore, the extension studies were limited by small sample sizes and were not sufficiently powered to determine statistical significance of efficacy and safety endpoints.

 Teduglutide is currently approved for PN-dependent SBS patients but few studies have explored its efficacy in broader malabsorptive disease states. Given the demonstrated cytoprotective actions of this peptide, we hypothesize that teduglutide use may be expanded to treat patients with altered surgical anatomy and/or chronic small bowel disease with functional short bowel syndrome, despite not meeting typical anatomical criteria or strict definition of intestinal failure. The following cases illustrate this thought process.

**Results**

**Case 1:**

 This is a 67 year old woman with a 30-year history of CD complicated by recurrent intra-abdominal abscesses with enterocutaneous and enteroenteral fistulae resulting in four small bowel resections and right hemicolectomy. She presented to our institution with a right lower quadrant abscess being drained by a catheter that was placed at an outside hospital two weeks prior. A small bowel follow-through study demonstrated small bowel extending only slightly past the jejunum. Clinically, the patient had chronic loose stools, intermittent abdominal pain, and required chronic vitamin supplementation. She was on prednisone 30 mg and mesalamine 1600 mgas maintenance therapy. She had persistent drainage and evidence of renal insufficiency secondary to dehydration. A CT scan demonstrated a fistulous communication between a right pelvic abscess and the adjacent sigmoid colon. Imaging also demonstrated a new cutaneous fistula adjacent to the drainage catheter. The patient’s nutritional evaluation was significant for hypomagnesaemia, hypophosphatemia, low pre-albumin of 10.4 mg/dl, evidence of Vitamin A and D deficiency, and an abnormal d-xylose absorption test with serum and urine xylose less than 5% of ingested. At this point, surgical intervention was deferred due to patient’s overall poor nutritional status. She was stabilized with IV fluid resuscitation, antibiotics, and vitamin supplementation. The patient was also started on TPN for 1-week during her inpatient stay that was continued upon discharge. The plan was to optimize her overall nutritional status and complete antibiotic therapy prior to further surgical intervention.

 The patient was also started on subcutaneous teduglutide three weeks after discharge to aid in nutritional recovery. After one month on teduglutide, she no longer required TPN and she demonstrated signs of abscess resolution allowing for removal of her drain. She reported improved appetite and noted decreased diarrhea and output from her enterocutaneous fistula. After about 10 months, there was complete clinical resolution of her enterocutaneous fistula and it was determined that surgical intervention was no longer required. In addition, her visceral protein stores returned to within normal limits during this period. She is currently continued on teduglutide and continues to do well nutritionally.

**Case 2:**

 This is a 48 year old female with CD who presented to our institution with progressively worsening chronic diarrhea, reporting about 6-12 episodes per day. She had also been experiencing intermittent fevers, chills, and generalized weakness at home and had lost 30 lbs in the past year. Her disease course was complicated by recurrent intra-abdominal abscesses and enterocolonic fistulae that have required multiple surgeries. At presentation, she was not on therapy for her CD, but she had previous trials with infliximab, adalimumab, azathioprine, corticosteroids, and methotrexate. A CT scan at that time illustrated a 6 cm intra-abdominal abscess, and a drainage catheter was placed. She had severe malnutrition with depleted visceral protein stores as seen by an albumin of 2.5 g/dl and prealbumin of 6 mg/dl. It was decided that the patient’s nutritional status should be optimized before potential surgery. The patient was subsequently approved for home TPN and was started on ustekinumab several weeks later.

 Despite TPN and initiation of treatment for her CD, six months later, the patient continued to have persistent fistulae and abscesses, and a trial of teduglutide therapy was started. The patient was able to wean off TPN shortly after starting teduglutide and by three months, her visceral protein stores improved as reflected by increases in total protein from 4.6 to 6.4 g/dl, albumin from 2.6 to 4 g/dl, and prealbumin from 8 to 23 mg/dl. Her BMI increased from 20 to 21. Surgical intervention has been postponed as the patient is doing well, and she is continued on teduglutide and ustekinumab.

**Case 3:**

 The is a 33 year old woman with CD complicated by multiple strictures, small bowel obstructions, and fistulae requiring several small bowel resections, including a 250 cm small bowel resection from post-operative complications in another country. She has had several trials of TPN starting at 14 years old that were never administered chronically due to multiple episodes of bacteremia within one month of starting TPN and one episode of fungemia that was complicated by liver failure and pancytopenia. She had been on multiple trials of pharmacological therapies, including corticosteroids, azathioprine, and infliximab. She presented to our institution with moderate-to-severe stricturing of her ileum, forming an inflammatory mass and obstruction that required an ileocecal bypass. Surgery resulted in approximately 120 cm of small intestine remaining with an intact ileocecal valve. Since then, she required multiple courses of antibiotics for small intestinal bacterial overgrowth and increased dietary supplementation. She struggled to maintain her normal body weight of 90-95 lbs. Her dietary status deteriorated significantly in the next year with her BMI declining from 18.0 to 15.9.

 Nutritional evaluation at that point demonstrated an increase in qualitative fecal fat, with evidence of vitamin A, D, and E deficiency as well as low visceral protein stores. The patient also had an abnormal d-xylose absorption trial with a urine and serum xylose level of less than 10% of ingested. She was started on teduglutide several weeks later to improve overall nutritional status without having to start TPN given prior life-threatening complications. After six weeks of teduglutide therapy, the patient gained weight, increasing her BMI to 17. She continued to gain weight with significant decrease in abdominal pain, bloating, and loose stools. About nine months later, she gained a total of 5 kg, maintaining her BMI at 19. Regarding maintenance therapy for her CD, the patient attempted trials of vedolizumab and certolizumab at that time, but she ultimately was continued on ustekinumab. Of note, the patient became pregnant at that point and was maintained on ustekinumab and teduglutide which provided improved nutritional support during her pregnancy. She never required parenteral support and is currently continued on teduglutide.

**Case 4:**

 This is a 33 year old man with paraplegia and a history of spina bifida complicated by a large non-healing stage IV sacral pressure ulcer. The patient had underwent multiple debridements in the past with limited improvement. The wound was noted to have chronic stool contamination and the decision was made to create a diverting ileostomy to assist in healing. In the next four years, the patient underwent several ileostomy revisions and 2 small bowel resections secondary to surgical complications that included recurrent ostomy leakage, abscess formation, and bowel perforation. After surgery, the patient struggled with intermittent high ileostomy output of greater than 2000 ml per 24 hours. At that time, he was admitted for severe dehydration, signs of malabsorption, and prerenal azotemia. The patient continued to report good oral intake and did not require parenteral nutrition. In spite of the diverting ileostomy, the patient’s decubitus ulcer continued to worsen and the patient was treated for osteomyelitis. Three months later, the patient was evaluated for possible decubitus flap reconstruction but the process was delayed due to his continued poor nutritional status. At the time, the decubitus wound measured 25 cm x 15 cm with exposure of the sacral bone. Clinical evaluation was significant for hypovitaminosis D, hyponatremia, hypomagnesaemia, hypocalcaemia, albumin of 1.1, and pre-albumin of 5.6.

One month later, the patient was started on teduglutide with the goal of improving nutritional status enough to control ileostomy output and ultimately allow for decubitus flap repair. The patient experienced mild symptoms of nausea at the start of therapy that was relieved with ondansetron. After a month, the patient’s overall health and nutrition improved with significantly decreased fluid requirements and vitamin supplementation, particularly magnesium oxide. The patient’s pre-albumin increased from 5.6 to 19.6 mg/dl over the course of therapy. A subsequent colonoscopy showed only segmental mild inflammation in the rectum and sigmoid colon secondary to diversion colitis with seeming resolution of previous fistula. Visualization through the ileostomy also showed normal appearing distal ileum with abundant villi. After two months of therapy, the patient stopped teduglutide due to persistent nausea. At the time of discontinuation, the patient’s ostomy output was significantly decreased and his decubitus ulcer on exam had decreased about 40% in size, measuring 15 cm x 10 cm, clean with granulation tissue, and without bone exposure. The wound remains improved four months after stopping teduglutide. On re-evaluation, it was decided that flap reconstruction would no longer be necessary, and the ulcer may only require a tissue grafting.

**Discussion:**

 Our own experience suggests that teduglutide might have an important role in the treatment of patients with moderate-to-severe CD by enhancing epithelial recovery. The mainstay of treatment for inflammatory bowel disorders has focused primarily on immunosuppression, but impaired epithelial repair is notably a vital element of its pathophysiology. In the first case, teduglutide was an effective adjunctive therapy in the management of CD complicated by fistulae, abscesses, and persistent malabsorption. Importantly, teduglutide was associated with the spontaneous closure of a colocutaneous fistula and reduction in its output. Notably, this marked improvement eliminated the need for surgical intervention. This effect is likely the result of significant improvement in nutritional status. The second case also demonstrated significant nutritional improvement, however the patient’s fistulae persisted. Nevertheless, teduglutide improved this patient’s candidacy for future surgical intervention. While indices of inflammation were not specifically measured, some studies have suggested in animal models that GLP-2 is also able to mediate anti-inflammatory action through vasoactive intestinal peptide (VIP) [7]. Further research should investigate teduglutide’s potential effects on chronic inflammatory states such as IBD. Both of these patients experienced continued symptomatic improvement while on teduglutide therapy and have thus far maintained independence from parenteral support.

 Teduglutide may also serve a role as a novel medication in management of non-PN dependent patients with malabsorptive disease. In the third case, although the patient met the requirements for resumption of TPN therapy, we were reluctant to revisit this therapy given multiple episodes of prior life-threatening complications. Administration of teduglutide in this patient dramatically improved nutritional status which later supported a healthy pregnancy to term. Furthermore, the patient with the high-output ileostomy in the fourth case demonstrated a dramatic increase in prealbumin after starting teduglutide that ultimately translated into decreased ostomy output and wound healing. Improving absorption of dietary peptides provides the positive nitrogen balance needed for healing in patients with altered surgical anatomy and/or chronic small bowel disease.

As CD is one of the most frequent causes of adult SBS, the use of teduglutide in patient populations that were excluded from the pivotal phase three studies warrants further investigation. However, current studies are limited. A randomized, placebo-controlled, dose-ranging pilot study was carried out on 100 patients with moderate-to=severely active CD [15]. Patients were randomized 1:1:1:1 to placebo or one of three doses of teduglutide (0.05, 0.10, or 0.20 mg/kg/day) delivered as a daily subcutaneous injection for 8 weeks. The primary outcome was response (Crohn’s Disease Activity Index (CDAI) decrease of ≥ 100 points) or remission (CDAI ≤ 150) at the end of 8 weeks. At completion, there was an optional 12-week open-label period of treatment with teduglutide 0.10 mg/kg/d. The results suggested that there was a dose-dependent reduction of the CDAI score with a trend toward increased response rate in the highest-dose teduglutide (0.20 mg/kg/d) group as early as week two; however, no statistical significance was observed compared to placebo as the study was underpowered. Notably, plasma citrulline levels at baseline for these patients with moderately active CD resembled that of patients with SBS or radiation enteritis and significantly increased following teduglutide administration, returning to normal levels and suggesting mucosal recovery. While this study investigated the efficacy of teduglutide in patients with CD unlike the phase three trials, it is important to note that patients requiring enteral or parenteral nutritional therapy were excluded. Additionally, this study suggests a dose-dependent response to teduglutide in patients with moderate-to-severe CD which was not shown in the phase three study of teduglutide use in SBS patients, although this may have been due to that study’s design [13]. Further clinical studies are needed with greater statistical power and more effective primary endpoints. Moreover, the optimal dosage of teduglutide in managing CD and inclusion of patients with severely active CD requiring enteral or parenteral nutritional support are also warranted. Nevertheless, this trial provided promising data for the use of teduglutide as a novel treatment of CD.

 Given its intestinotrophic and cytoprotective effects, teduglutide may have a role in perioperative intestinal rehabilitation and as adjunctive therapy in both IBD patients and in patients with functional short bowel syndrome not meeting strict criteria for intestinal failure. We urge further research in this area. Like other candidate growth factors, there exist theoretical concerns for adenoma or carcinoma development with long-term teduglutide therapy. Therefore, current recommendations include a baseline colonoscopy prior to receiving therapy, a repeat exam at 1-year, and follow up exams about every 5 years thereafter or more often as needed. Larger prospective studies should be conducted to assess teduglutide efficacy and safety in other treatment populations. A 10-year prospective database, of which our institution is a part, has been established by the manufacturer Shire-NPS Pharmaceuticals, Inc. to better understand and detect adverse events of long-term teduglutide therapy in PN-dependent SBS patients (Clinicaltrials.gov identifier: NCT01990040).

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