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The Polish Intestinal Failure Centres' consensus on the use of teduglutide for the treatment of short bowel syndrome

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ABSTRACT

Objective: Teduglutide is an active, glucagon-like peptide (GLP)-2 analog with proven clinical efficacy regarding intestinal adaptation in patients with short bowel syndrome (SBS). There are two factors that preclude its reimbursement, and thereby, its availability: its cost (reaching ~$300,000/y)—which significantly exceeds the cost of home parenteral nutrition (HPN) in most countries—and the lack of clear guidelines. The aim of this study was to create evidence-based working criteria for the use of teduglutide that could be used in clinical settings.
Methods: Experts from the Polish Network of Intestinal Failure Centers analyzed available research and considered experience on the topic of HPN and intestinal failure to create guidelines.
Results: Experts agreed that there are two groups of HPN patients who can benefit from therapy with a GLP-2 analog: those with a good prognosis (in whom complete weaning from HPN may be possible) and those with a poor prognosis (the therapy would be lifesaving). Patient criteria comprise the following: inclusion and exclusion criteria, parameters that can be used for monitoring, outcome measures, and the rationale for the termination of the treatment.
Conclusions: It was possible to describe inclusion criteria for both patient groups that justify the use of teduglutide from medical and economic perspectives.

Introduction

Teduglutide is an active, glucagon-like peptide (GLP)-2 analog with proven clinical efficacy regarding intestinal adaptation in patients with short bowel syndrome (SBS) [1,2]. There are two factors that preclude its reimbursement, and thereby, its availability: its cost (reaching ~$300,000/y)—which significantly exceeds the cost of home parenteral nutrition (HPN) in most countries—and the lack of clear guidelines.

For these reasons, a group of experts from the Polish Network of Intestinal Failure Centers decided to prepare inclusion criteria for the use of teduglutide in patients with SBS, using available data from research papers and personal experience from clinical trials and the treatment of intestinal failure (IF).

Methods

The panel of experts was established by leaders of IF units from all five Polish IF units, forming the Polish Network of Intestinal Failure Centers. Three of these centers participated in Phase II clinical studies of the GLP-2 analog, which occurred between 2008 and 2013 [1].

Shire (Shire International, GmbH, Germany) facilitated some of the experts' meetings by covering expenses. MK was the coordinator of the working group and also contributed to the writing of the manuscript. SK participated in the working group and was responsible for the conception and the design of the manuscript. JS participated in the working group and contributed to the writing of the manuscript. KM, KK, and KU participated in the study group and contributed to the preparation of the guidelines. The authors have no conflicts of interest to declare.

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The study was divided into two phases. During the first phase, occurring between November 1, 2015 and January 31, 2016, a literature search on teduglutide was performed. The aim was to analyze reported dosages, contraindications, adverse effects, and clinical outcomes.

A literature search was performed using following data sources: MEDLINE, Embase, Cochrane Register of Controlled Trials. Search terms *glp-2, glcagon-likepeptide 2, teduglutide*, and *intestinal failure* were used.

During the second phase, between February 1 and March 31, 2016, comprehensive criteria were prepared to define the group of patients that might benefit from treatment with teduglutide and for whom its use would be cost-effective from medical or economic perspectives, or a combination of both.

Experts decided that there were two groups of patients on HPN who might benefit from teduglutide therapy: those with a good prognosis for weaning off HPN and those with HPN complications, in whom teduglutide therapy might be lifesaving.

In all cases, the inclusion and exclusion criteria, parameters for monitoring treatment, outcome measures, and rationale for treatment termination were established.

Results and discussion

Phase 1: The analysis of the clinical value of teduglutide

Basic clinical studies undoubtedly proved the effectiveness of teduglutide because its use promoted the expansion of the intestinal mucosa [3]; inhibited gastric acid secretion and gastric emptying, and increased intestinal blood flow and intestinal barrier function [4–9]; and enhanced nutrient and fluid absorption [10,11].

Furthermore, the following clinical studies proved that teduglutide helps reduce the volume of parenteral nutrition (PN) in patients on HPN:

- The clinical efficacy of teduglutide in SBS was assessed in an open-label, Phase II pilot study and afterward in a multicenter, multinational, randomized, placebo-controlled, double-blind, Phase III study [1,12];
- The absolute intestinal wet weight absorption in 15 of 16 patients was increased after 21 d of treatment. The average increase in wet weight absorption was 743 ± 477 g/d ($P < 0.001$). The scale of the wet weight absorption was similar for patients with end-jejunostomy and with >50% of the colon in continuity [1,2,12];
- Fecal wet weight decreased significantly compared with baseline in the entire group of patients (711 ± 734 g/d; $P = 0.001$) [1,2,12];
- A significant improvement in absolute energy absorption and relative energy absorption were observed [1–3]; and
- A reduction of the volume of HPN per week was observed. The range was a 20% reduction up to complete weaning off HPN [1,2]. The effect was significantly higher in the treatment group than in the placebo group (46% versus 6%), and the mean dose reduction was 2.5 L/wk [1,2].

Phase 2

Using the aforementioned data, the following conclusions were drawn and used for the formulation of treatment criteria, also presented in Tables 1 and 2

- Age >18 y: Teduglutide was analyzed only in adults; moreover, it was registered for this age group.
- Dosage: Two different dosages were used for the aforementioned studies; however, the subcutaneous injection of 0.05 mg/kg daily was proven to be the most beneficial. The response rates were significantly higher with the teduglutide dosage of 0.05 mg/kg daily than in the placebo group (46% versus 6%; $P > 0.005$) [1,2,12].
- PN optimization and stabilization: In the most credible studies, patients went through a period of PN optimization for a maximum of 8 wk, during which the goal was to establish a baseline of minimal tolerated PN volume that resulted in a urine output of 1 to 2 L/d. This period was followed by a 4- to 8-wk period of PN stabilization [1,2,12].
- Adverse events (AEs) during treatment: In almost all patients, the use of teduglutide was safe and well tolerated. The most common AEs were abdominal pain (24%), headache (24%), nausea (22%), nasopharyngitis (16%), and vomiting (15%). The most frequently reported serious AEs included catheter-related complications, catheter sepsis, catheter site infection, small intestinal obstruction, and fever [1].
- Weaning-off algorithm: A strict parenteral weaning algorithm was used in the aforementioned studies. The protocol allowed for ≤10% reduction in parenteral volumes at 4-wk intervals. Weaning was performed if the 48-h urinary volumes exceeded baseline values by >10%, regardless of the absolute amount. Higher reductions were allowed only if the urinary volumes exceeded 2.0 l L/d [2].
- PN volume <12 L/wk: The reduction of dependency on PN was proven in most patients during the Phase III trials, but the best results were observed in patients with a gastrointestinal (GI) tract in continuity and the presence of the large bowel, receiving <7 L of intravenous (IV) fluids per week. A significant reduction in the PN volume was noted if the provision was <15 L/wk [1,2,13–19]. In patients who regained GI tract autonomy, the mean PN intake was ~13.4 L/wk [20]. The mean reduction of IV fluids was 4.4 L (placebo: 2 L) and 1 d/wk of HPN [2].
- The length of the remaining small intestine to be no smaller than 120 cm in the case of end-ileo-cutaneostomy or no limit in case of retained GI tract continuity, or a citrulline concentration <20 μmol/L, assessed 24 mo after the last reconstructive surgery.

Symptoms of SBS include diarrhea, weight loss, and water and electrolyte imbalances. After the resection of the proximal part of the small bowel, the remaining distal part takes over its function; but after the resection of the distal part, the proximal cannot replace its functions [21]. The resection of the ileocecal (Bauhin's) valve shortens the flux of nutrients and increases the risk of bacterial overgrowth [21]. Many authors noted that intestinal rehabilitation is impossible and there is a lifelong dependency on PN if the length of the remaining small intestine, starting from the ligament of Treitz, is <100 cm in cases of end-ileostomy, <65 cm in cases in which the small intestine was anastomosed to the left colon, and <35 cm in cases in which the small intestine was anastomosed to its distal part and the Bauhin's valve is intact.

If there is no information regarding the length of the remaining GI tract in the patient's medical history, an imaging examination should be performed. The latter can include the following: contrast agent–enhanced x-ray, computed tomography, magnetic resonance imaging, and endoscopy. The serum citrulline concentration also can be helpful in the assessment of GI tract function as it is a sensitive test for enterocyte function. The lower threshold for citrulline that indicates proper absorptive capacity is >20 μmol/L [22,23].

- The lack of potential for further reconstructive surgery of the GI tract, and the presence of HPN dependency for at least the