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TRANSLATIONAL MEDICINE: BENCH TO BEDSIDE

Hormonal Management of Small Bowel Failure

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Short bowel syndrome (SBS) is characterized by severely reduced functional intestinal length: <150–200 cm of post-duodenal small intestine.[1] Due to diminished absorptive capacity from reduced intestinal length, conventional diet does not always adequately provide nutrition for short bowel syndrome patients. Consequently, many patients rely on total parenteral nutrition. These patients often experience intestinal failure (IF), which has been defined as "loss of absorptive capacity characterized by the inability to maintain proper hydration or protein energy, electrolyte, or micronutrient balances while on a conventional diet".[2]

IF associated with SBS presents as severe diarrhea, abdominal pain, dehydration, and malnutrition. The patients dependent on parenteral nutrition also experience complications such as catheter-related infections, catheter thrombosis, and liver failure, which increase their morbidity and mortality.[3,4]

Early surgical reports in critically ill patients suggest that growth hormone (GH) was of benefit in surgical adaptation and weaning from parenteral nutrition in SBS patients.[5] However, more recent reviews concluded the effects of GH were "transient and short lived", and overall the data were "inconclusive regarding the effectiveness of this therapy".[6] Animal models suggest suppressors of cytokine signaling (SOCS-2), a post-receptor mediator of GH signaling, may inhibit intestinal crypt cell proliferation in response to GH or IGF-1 induced by GH, thus blunting its proliferative effect on the intestinal crypt over time.[7]

However, glucagon-like peptide-2 (GLP-2) agonists, and more recently, glucagon-like peptide-1 (GLP-1) agonists have been used to increase nutrient and fluid absorption and partially or completely ameliorate the use of parenteral nutrition (PN) in SBS patients. The modulation of motility for GLP-1 and the trophic effects for GLP-2 agonists, respectively, have shown improvement in fecal wet weight and energy absorption with improved post-prandial glucose profiles.[8]

GLP-2 receptor, a G-protein-coupled receptor, has been found in enteroendocrine cells of the distal intestine, but not on crypt and or villus cells, suggesting GLP-2 trophic effects on these structures is mediated by other growth factors such as keratinocyte growth factor or insulin-like growth factor-1.[9] Teduglutide, a modified version of GLP-2, was shown to increase villus height and crypt depth by 50% in SBS patients and to increase both fluid and macronutrient absorption.[10]

GLP-1 levels rise in response to increases in luminal glucose and fatty acids. It is produced by L-cells of the ileum, which then binds to the GLP-1 receptor expressed in target tissues like the stomach and small intestine smooth muscle.[11] By inhibiting gastric emptying and delaying small bowel motility, it significantly contributes to the ileal "brake" phenomenon, thereby facilitating nutrient absorption.[12] In a pilot study of five SBS patient, exenatide—a GLP-1 agonist—enabled reduction in diarrhea in all subjects and three (60%) were even able to discontinue PN.[13]

Two recent articles highlight the effectiveness of using pharmacologically modified GLP agonists in the medical management of SBS with IF. By substituting a critical alanine residue in the N-terminal portion of the hormone, it renders them resistant to dipeptidyl peptidase-4 (DPP-4) degradation and creates a potent drug with significantly prolonged duration of action of 18-24 h rather than minutes for the unmodified peptide.

The use of GLP-2 agonists is reviewed in Schwartz, *et al.*[14] titled "Long-Term Teduglutide for the Treatment of Patients with Intestinal Failure Associated with Short Bowel Syndrome." This study involved a 2-year, open-label trial STEPS-2—designed to evaluate the efficacy and long-term safety of teduglutide.[14] Prior to this STEPS-2 trial, a 24-week, phase III, placebo-controlled trial concluded that using teduglutide could significantly reduce PN requirements in SBS patients.[15] Hence, a total of 65 patients who had either completed this 24-week, phase III study or initially qualified for it but were not treated subsequently enrolled and completed the STEPS-2 trial. After receiving subcutaneous teduglutide 0.05 mg/kg per day for an additional 24 months, PN volume reduction from baseline was quantified. Significant clinical response to teduglutide was defined as 20–100% reduction from baseline in weekly PN volume.[14] Ninety-three (93%) percent of patients who received teduglutide for both the phase III and the STEPS-2 trial achieved clinical response. Fifty-five (55%) percent of patients who received a placebo for the phase III trial but received teduglutide for the STEPS-2 trial achieved clinical response. Sixty-seven percent (67%) of patients who received no treatment for the phase III trial but received teduglutide for the STEPS-2 trial achieved clinical response. Thirteen patients achieved full enteral autonomy.[15]

In patients with SBS, the use of teduglutide is now widely accepted as effective treatment in PN-dependent patients who have failed weaning attempts after 6 month of intestinal adaptation. Barriers to treatment in the United States are significant costs

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(~$300 K yr) but an orphan drug consortium has been created to cover the out of pocket cost so that direct patient costs are typically less than $500 per year.

Partly in response to these high costs, there have been attempts to utilize GLP-1 agonists or in combination with GLP-2 agonists. The following article discusses the use of liragluitide—a novel GLP-1 agonist. The article is titled "Effect of Liraglutide Treatment on Jejunostomy Output in Patients With Short Bowel Syndrome: An Open-Label Pilot Study" by Hvistendahl *et al.*[16] In this pilot study involving 8 patients with end-jejunostomy, liraglutide was administered subcutaneously once daily for 8 weeks. Consequently, ostomy wet weight output was reduced by 15% ($P = .049$). Intestinal wet weight absorption increased by 92% ($P = .05$), with concomitant increased urine production of 66% ($P = 0.02$), and intestinal energy absorption improved by 902 kJ per day or 22% ($P = 0.02$).[16] Hence, these antimotility GLP-1 agonists show promise as substitutes or adjuncts to GLP-2 therapy.

Surgical efforts to restore continuity between residual small intestine and residual colon following a catastrophic resection may in combination with or without GLP II therapy successfully allow weaning from PN. Appropriate referral to centers specializing in both intestinal rehabilitation and short bowel surgery, including small bowel transplant should be emphasized in the long-term management and care of these patients.

CONFLICT OF INTEREST

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