Teduglutide and Pediatric Short Bowel Syndrome

Pediatric short bowel syndrome (SBS) is associated with intestinal failure, prolonged parental nutrition (PN) use, impaired quality of life, and increased morbidity and mortality. Teduglutide is a glucagon-like peptide that may prevent some of the clinical complications of SBS by subsequent hormonal effects including increased epithelial proliferation of crypts and prolonged intestinal motility time to improve intestinal absorption and adaption.

The authors of this study performed a multi-center, open-label study using teduglutide as a treatment of pediatric SBS. Enrolled patients were between 1 and 17 years of age and had to have a diagnosis of SBS defined as using PN for at least 30% of caloric intake without any decrease in PN or increase in enteral nutrition (EN) for at least 3 months. Patients receiving teduglutide dosing were divided into 3 cohorts receiving subcutaneous teduglutide at 0.0125, 0.025, or 0.05 mg/kg/day dosing for 12 weeks. Additionally, patients were enrolled sequentially into groups of increased dosing, and all patients were monitored weekly for the first 4 weeks of the study, followed by monitoring every 2 weeks until the study was complete. These patients were compared to a control group who received standard SBS care. Monitoring included serum testing of electrolytes, liver enzymes and other serum tests; changes in PN requirements as well as EN tolerance; and recording of adverse events. Most study subjects experienced an adverse event during the study (95% of patients receiving teduglutide and 100% of patients receiving standard of care). Vomiting was the most common adverse event in patients receiving teduglutide, which had increased frequency with higher dosing.

The study included 42 patients in which eight were in the 0.0125 mg/kg/day dosing group, 14 were in the 0.025 mg/kg/day dosing group, and 15 were in the 0.05 mg/kg/day dosing group. An additional five patients were followed separately as the control group that did not receive teduglutide. Adult study adverse events, such as intestinal obstruction, did not occur in this pediatric trial, and no patients had to discontinue teduglutide. Decreased PN requirements occurred in patients receiving teduglutide at 0.025 mg/kg/day (41% decrease in PN volume and 45% decrease of PN calories defined as kcal/kg/day) and 0.05mg/kg/day (25% decrease in PN volume and 52% decrease of PN calories). EN tolerance also increased in all three teduglutide dosing groups (22% in patients receiving 0.0125 mg/kg/day, 32% in patients receiving 0.025 mg/kg/day, and 40% in patients receiving 0.05 mg/kg/day). Four of the patients receiving teduglutide were able to wean off PN during the study although two of these patients were placed back on PN at four weeks after the study ended. Serum citrulline levels were widely variable during the study although the median citrulline levels in all three teduglutide dosing groups increased during the study.

This study shows the potential of teduglutide as a treatment of pediatric short bowel syndrome; however, larger studies are needed to determine if the medication's effect remains beneficial long term without the presence of a significant side effect profile.

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Disease Prediction Modeling in Pediatric Crohn's Disease

Pediatric Crohn's disease (CD) can be associated with intestinal complications including stricturing and penetrating disease, and the authors of this study evaluated potential risk factors for such complications in children by using data from the multi-center Risk Stratification and Identification of Immunogenetic and Microbial Markers of Rapid Disease Progression in Children with Crohn's Disease (RISK) study. The RISK study enrolled pediatric patients with CD as well as control patients who had no inflammation on endoscopic biopsy, and all patients underwent microbial as well as gene expression analysis. The use of anti-tumor necrosis factor alpha (anti-TNF alpha) was documented in patients, and early anti-TNF alpha therapy was defined as occurring within 90 days of CD diagnosis with such patients undergoing induction dosing and at least one maintenance dose. CD location and behavior was evaluated using the Montreal classification system in order to classify structuring and internal penetrating disease. Standard serum testing for CD was obtained, and all patients had RNA and DNA sequencing from ileal and rectal biopsies as well as DNA sequencing of stool samples.

In total, 913 patients were enrolled in the study for which 62% of patients were male, and the median age at time of CD diagnosis was 12.4 years. Stricturing disease was present in 54 patients; penetrating disease was present in 24 patients. Patients who received anti-TNF alpha therapy within 90 days of a CD diagnosis were significantly less likely to have penetrating complications although this effect was not seen for stricturing complications. CBir1 seropositivity was significantly associated with stricturing outcomes; older patient age, ASCA IgA and CBir1 seropositivity, and African American race was significantly associated with penetrating outcomes. Fourteen bacterial genera were associated with CD, and *Rothia* and *Ruminococcus* were associated with stricturing disease while *Collinsella* was associated with penetrating disease. Increased signaling for *Veillonella* was present in the terminial ileum. Human genes signaling extracellular matrix accumulation were present in patients with stricturing disease while inflammatory response genes to bacterial infection were present in patients with penetrating disease.

This study demonstrates that early anti-TNF alpha use in pediatric patients with CD reduces the risk of penetrating complications such as abscess formation. Furthermore, the clinical characteristics of patients with the associated bacterial genera results and human gene signaling may allow for clinical modeling paradigms to improve CD patient outcomes as well as development of new therapies for this disease.

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