Emerging Therapies in Intestinal Failure

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DISCLOSURE

I have no pertinent financial relationship with a commercial entity producing health-care related products and/or services.
Residual jejunal ileal length in cm.

Ileocecal valve intact

Ileocecal valve resected

Alive
Dead
Logistic Analysis Curve: Theoretical Relationship between Odds of Weaning from PN and Residual SB length

Andorsky, et al., J Pediatr 2001; 139:27
New Approaches

• Serial transverse enteroplasty (STEP)
• Staging with gut biomarkers
• “Early” endoscopy
• Glutamine
• Probiotics
• Omega 3 fatty acids
• Growth Factors
  – Growth hormone
  – GLP-2 and its analog, Teduglutide
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Citrulline Metabolism

Citrulline in SBS

Relationship to PN dependence

Minimum Citrulline Significantly Lower in Patients with CRBSI

Minimum Serum Citrulline (µmol/L)

CRBSI (n = 26)  
No CRBSI (n = 25)

P = .004, Student t-test

6.7  11.3

Hull et al., JPEN 2011
Serum Citrulline, Catheter Duration, and CRBSI

Minimum Citrulline
- 5 µmol/L
- 10 µmol/L
- 15 µmol/L
- 20 µmol/L

Probability of CRBSI (%) vs. Duration of Catheter (months)
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High diagnostic yield of gastrointestinal endoscopy in children with intestinal failure

Y. Avery Ching\textsuperscript{a,b,*}, Biren P. Modi\textsuperscript{a,b}, Tom Jaksic\textsuperscript{a,b}, Christopher Duggan\textsuperscript{a,c}

• 27 SBS patients, 61 GI endoscopies
• 43/61 had abnormal findings:
  – Infectious (20%)
  – Anatomic (18%)
  – Peptic (15%)
  – Allergic (15%)
• 24/27 patients had at least one finding
Anastomotic Ulceration

- **Hx:** intestinal atresia
- **Sx:** GI bleeding
- **Findings:** anastamotic ulcerations
- **Dx:** anastamotic ulcerations
- **Management**
  - Sulfasalazine
  - Small bowel resection
Bacterial Overgrowth

- Hx: intestinal atresia
- Sx: feeding intolerance
- Findings: ulcerations and villous atrophy
- Dx: Bacterial overgrowth
- Management: tailored antibiotic regimen
Allergic Colitis

- **Hx:** segmental volvulus
- **Sx:** GI bleeding
- **Findings:** patchy erythema and exudates; >15 eos per HPF
- **Dx:** allergic colitis
- **Management:** allergen-free diet
Impact on Clinical Management

• 20 patients (74%) had a change in clinical management following initial endoscopy
• Surgical intervention
  – Stricturoplasty, small bowel resection
  – Serial transverse enteroplasty
• Change in medication
  – Tailored antibiotic coverage
  – Started proton-pump inhibitors
  – Started sulfasalazine
• Change in diet
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Glucagon-like peptide 2

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<td>Glicentin</td>
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<td>IP-2</td>
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? Increases SB mass  glucose control  intestinotrophism  appetite
Trophic Effect of GLP-2 Infusion in TPN-fed Newborn Piglets

Burrin et al.
GLP-2 in Murine Enteritis

• 7-9 week old mice
• Pre- and/or post-treated with GLP-2 or vehicle with indomethacin-induced enteritis
• Mortality, histology, cytokine levels, bacterial cultures

Boushey et al., Am J Physiol 1999; 277: E937-947
GLP-2 increases villus height and crypt depth in mice given NSAIDs.
GLP-2 reduces bacterial translocation in mice given NSAIDs

Boushey et al., Am J Physiol 1999; 277: E937-947
Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients

• 16 adults with SBS
  – Mainly Crohn’s disease, most > 5 years post-op
  – 10 w/ end jejunostomies, 6 with colon
• Received 0.03 – 0.15 mg/kg/d SQ x21d
• Baseline, treatment and follow-up studies

Jeppesen et al., Gut 2005; 54:1224
- 711 g fecal wet weight
+ 751 g gut absorption
+ 555 g urine output
+ 8% energy absorption (NS)
+ crypt depth, villus height

Figure 1  Faecal wet weight, intestinal wet weight absorption, and urine weight in individual patients in group 1 at baseline (B, days -3 to 0), during treatment (T, days 18–21), and at follow up (F, days 39–42).

Jeppesen et al., Gut 2005; 54:1224
Nycomed Confirms Commitment to GATTEX(TM) Partnership; NPS Pharmaceuticals, Inc. (NPSP) to Receive $25 Million Payment

BEDMINSTER, N.J., Oct. 31 /PRNewswire-FirstCall/ -- NPS Pharmaceuticals, Inc. announced today that Nycomed, after an in-depth review of the results from the recently completed Phase 3 study in Short Bowel Syndrome, has confirmed its intention to proceed with the development and commercialization of GATTEX(TM) (lendedulutide) outside North America. Under the terms of the partnership agreement signed in September, Nycomed will pay NPS the $25 million up-front payment balance due and receive licensing rights to develop and commercialize GATTEX outside the United States, Canada and Mexico for the treatment of gastrointestinal disorders. NPS will retain the right to develop and commercialize GATTEX in North America.
Teduglutide, a Novel Analogue of Glucagon-like Peptide 2 (GLP-2), Is Effective and Safe in Reducing Parenteral Support Volume in Short Bowel Syndrome–Intestinal Failure Subjects: Results From a 24-Week, Placebo-Controlled Phase 3 Trial (STEPS)
Palle B. Jeppesen, Marek Pertkiewicz, Douglas L. Seidner, Stephen O'Keefe, Hartmut Heinze, Bo Joelsson
Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome

P B Jeppesen,¹ R Gilroy,² M Pertkiewicz,³ J P Allard,⁴ B Messing,⁵ S J O’Keefe⁶

- 83 subjects with SBS randomized to 24 weeks of placebo or 0.05 or 0.10 mg/kg/d of teduglutide SC
- Algorithm-driven PN weaning depending on urine output
- Graded response score = primary outcome variable
Safety and Efficacy of Teduglutide After 52 Weeks of Treatment in Patients With Short Bowel Intestinal Failure

STEPHEN J. D. O’KEEFE,* PALLE B. JEPPesen,† RICHARD GILROY,§ MAREK PERTKIEWICZ,‖ JOHANE P. ALLARD,¶ and BERNARD MESSING#

*Division of Gastroenterology, University of Pittsburgh, Pittsburgh, Pennsylvania; †Department of Medical Gastroenterology, Rigshospitalet, Copenhagen, Denmark; §Department of Gastroenterology, University of Kansas Medical Center, Kansas City, Kansas; ‖Department of General Surgery and Clinical Nutrition, Medical University of Warsaw, Warsaw, Poland; ¶Division of Gastroenterology, University of Toronto, Toronto, Ontario, Canada; #Hôpital Beaujon Service de Gastroenterologie et Assistance Nutritive, Clichy, France
Figure 1. Flow chart for the 52-week efficacy and safety analysis. Patients who received placebo treatment in the initial 6-month RCT are not included in this report.
Figure 2. Mean reduction in parenteral support over 52 weeks for the 2 dose levels of teduglutide. Patients enrolled in the extension study were continued on teduglutide at the same dose as they were given during the RCT.

O’Keefe SJD et al., Clin Gastro Hepatol 2013
RESULTS: The most common adverse events reported included headache (35%), nausea (31%), and abdominal pain (25%); 7 patients withdrew because of adverse events (gastrointestinal disorders in 4). Both groups had progressive reduction in PN. At week 52, 68% of the 0.05-mg/kg/d and 52% of the 0.10-mg/kg/d dose group had a ≥20% reduction in PN, with a reduction of 1 or more days of PN dependency in 68% and 37%, respectively. Four patients achieved complete independence from PN.

CONCLUSIONS: For patients with short-bowel syndrome intestinal failure, the efficacy of teduglutide was maintained over 52 weeks and the safety profile was sufficient for it to be considered for long-term use. Further studies are needed to determine whether these effects will translate into improved quality of life and reduced PN complications. ClinicalTrials.gov number, NCT00172185.
Center for Advanced Intestinal Rehabilitation at Children’s Hospital Boston