Short Gut

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Disclosures

AFFILIATION/FINANCIAL INTERESTS	
Grants/Research Support:	VectivBio (JT)
Scientific Advisory Board/Consultant:	Takeda Inc (YA)
Speakers Bureau:	
Stock Shareholder:	
Other Financial or Material Support / Honorarium:	

CanMEDS roles covered

√	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
	Communicator (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
√	**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
	Leader (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
√	**Health Advocate** (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
	Scholar (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
	Professional (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

Objectives

- Become familiar with the clinical trials data in adults and children with short gut for the commercially available glucagon like peptide-2 analogue

- Understand the potential benefits and risks in considering glucagon like 2 peptide treatment for patients with short gut

- Be able to diagnose and treat children with intestinal failure associated liver disease and advanced non-cholestatic liver fibrosis

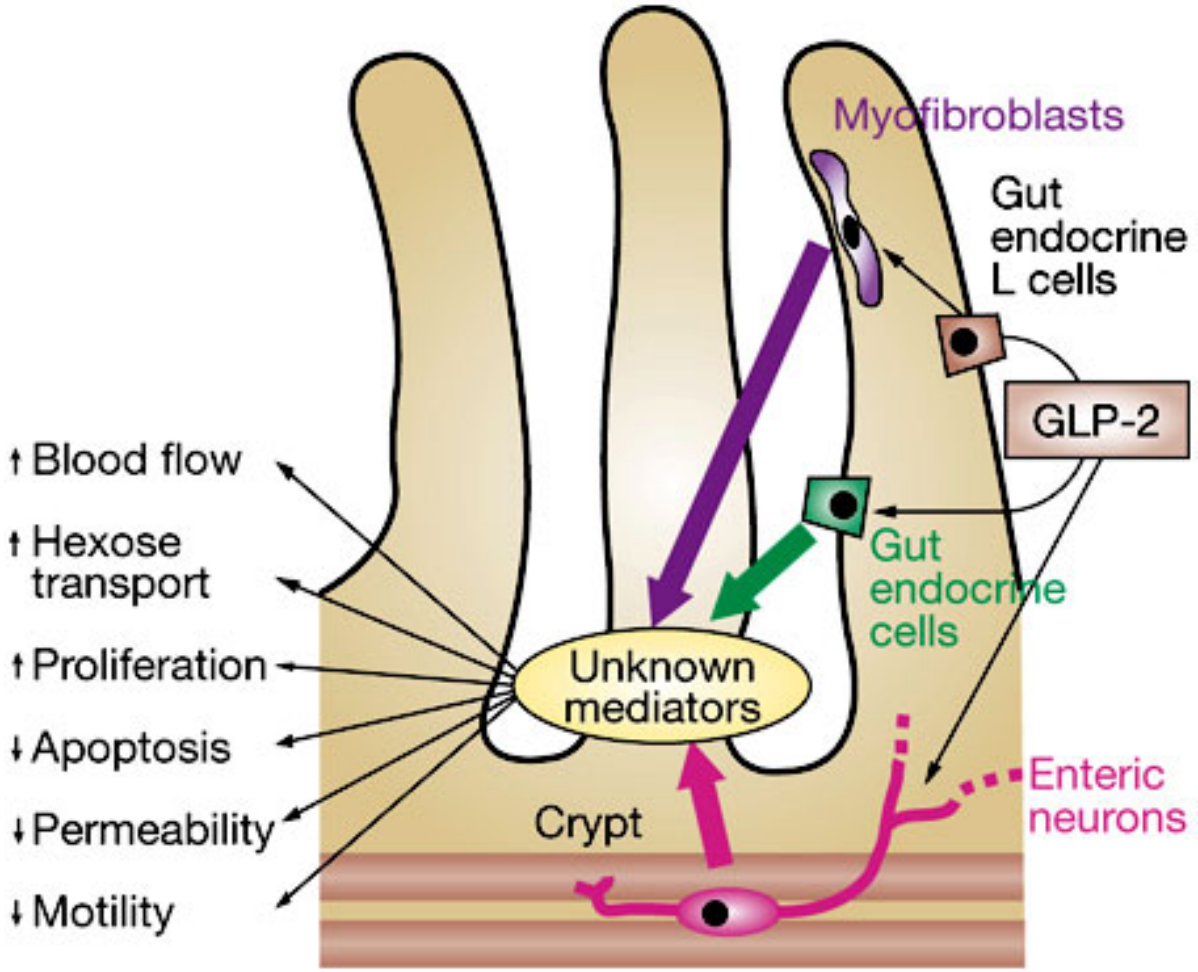
A Patient

- 3 year old survivor with short gut
- Ex 33 weeks, NEC 25cm jejunocolic anastomosis
- 9 hospital admissions to date
- EN: 20% of calories. Small amount of solids.
- PN x 18hrs; 7 nights [80% of calories].
- Stool output 40cc/kg/day

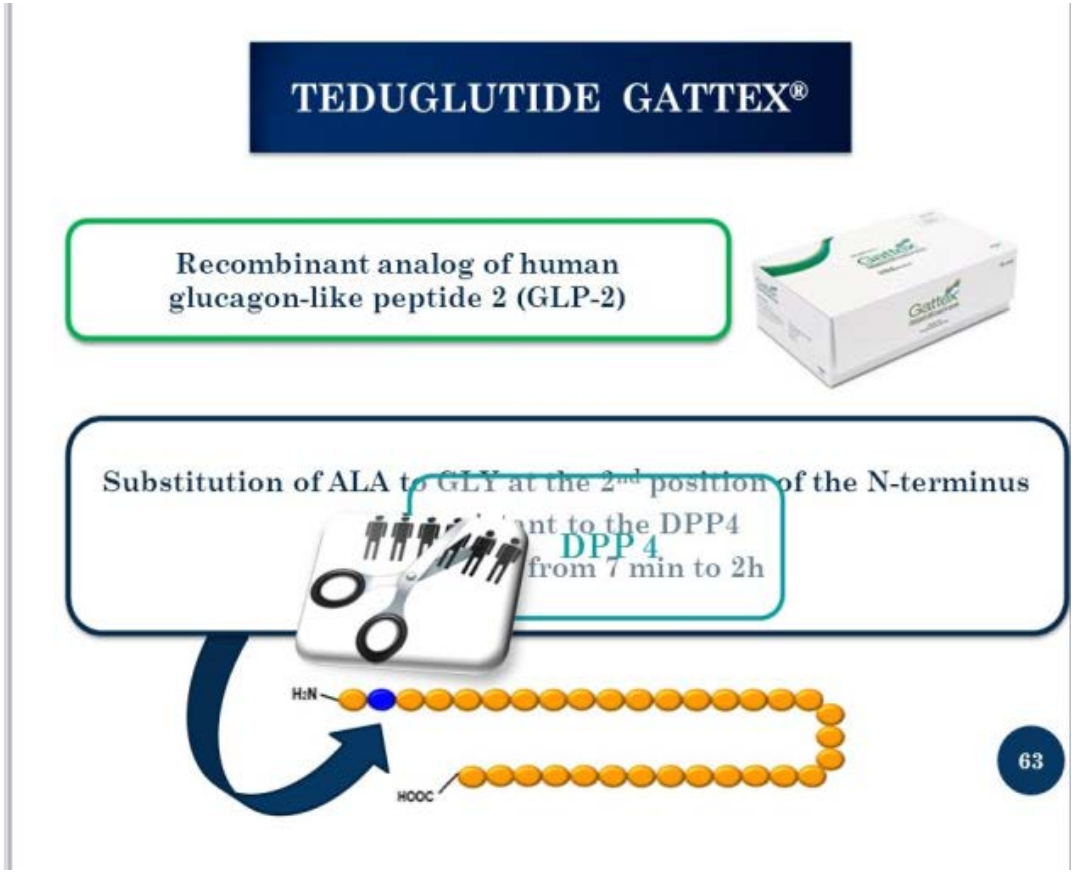
Would a glucagon like peptide 2 analogue help

Physiology: GLP-2 in the gut

- Trophic
- Slow motility
- Nutrient absorption
- Gut Permeability
- Anti-inflammatory



Drug discovery & Approval



- 2000 Orphan drug approval US
- 2012 Approval short gut adults US & Europe
- 2016 Approval short gut adults Canada
- 2016 Extension to short gut children Europe
- 2019 Extension to short gut children US & Canada

Health Canada

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

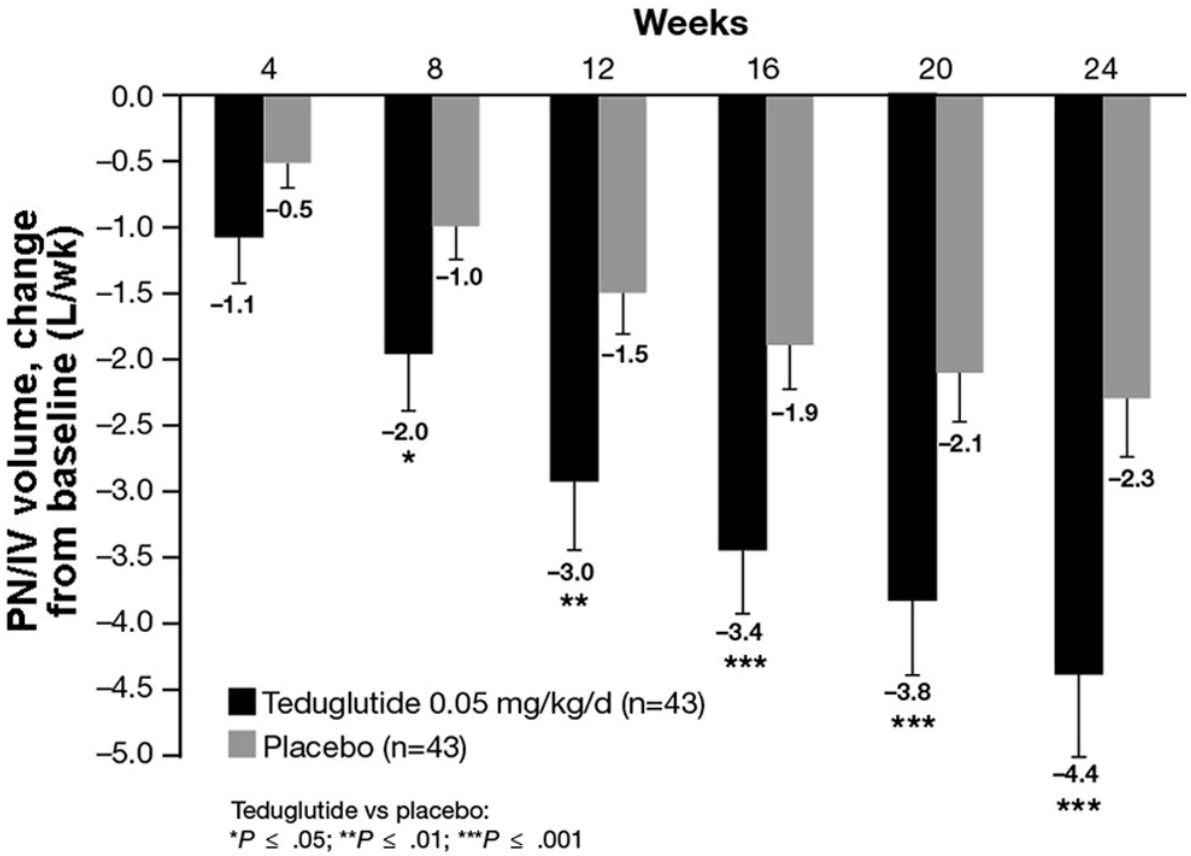
Confirmatory Phase 3 study adults

GASTROENTEROLOGY 2012;143:1473–1481

CLINICAL—ALIMENTARY TRACT

Teduglutide Reduces Need for Parenteral Support Among Patients With Short Bowel Syndrome With Intestinal Failure

PALLE B. JEPPESEN,* MAREK PERTKIEWICZ,‡ BERNARD MESSING,§ KISHORE IYER,‖ DOUGLAS L. SEIDNER,¶ STEPHEN J. D. O'KEEFE,# ALASTAIR FORBES,** HARTMUT HEINZE,‡‡ and BO JOELSSON§§



63% treatment vs 30% placebo responded

≥1 day reduction PS 54% treatment vs 23% placebo

Absolute volume decrease in PS 32% treatment vs 23% placebo

Higher response rates if colon in continuity

Overall autonomy

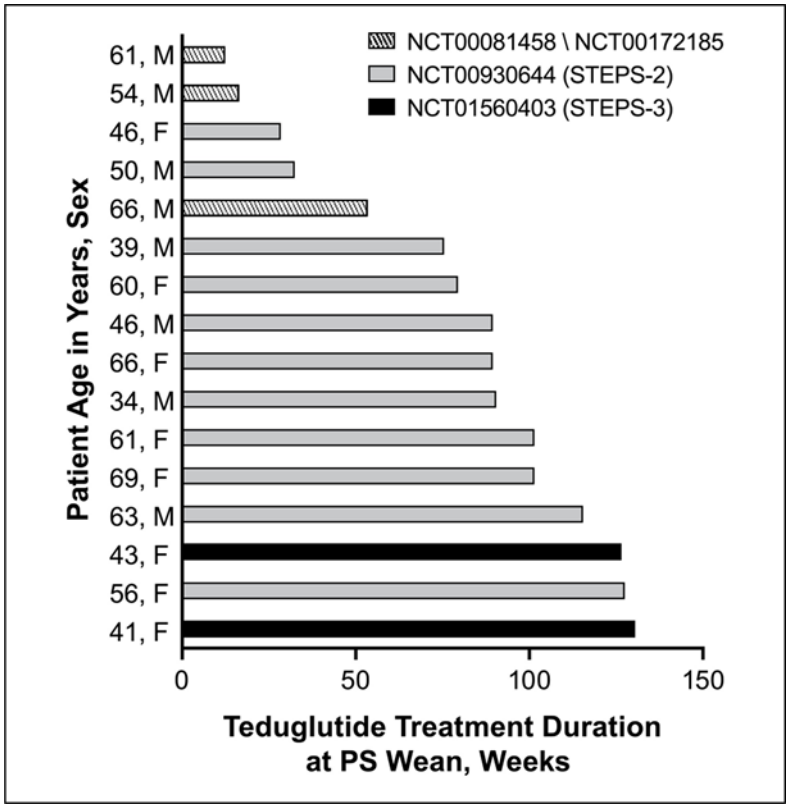
- 16/134 (12%) patients in pooled trial data achieved autonomy from PN
- After a median of 5 years (2-18 years) of PN
- Small intestinal length 26-250cm
- 12/16 colon in continuity
- No patients in the placebo group weaned from PN support

Independence From Parenteral Nutrition and Intravenous Fluid Support During Treatment With Teduglutide Among Patients With Intestinal Failure Associated With Short Bowel Syndrome

Journal of Parenteral and Enteral Nutrition
Volume 41 Number 6
August 2017 946–951

DOI: 10.1177/0148607116680791

Kishore R. Iyer, MBBS, FRCS, FACS[1]; Marek Kunecki, MD[2]; Joseph I. Boullata, PharmD, RPh, BCNSP[3]; Ken Fujioka, MD[4]; Francisca Joly, MD, PhD[5]; Simon Gabe, MD[6]; Ulrich-Frank Pape, MD[7]; Stéphane M. Schneider, MD, PhD, FEBGH[8]; María Nuria Virgili Casas, MD, PhD[9]; Thomas R. Ziegler, MD, MS[10]; Benjamin Li, MS[11*]; Nader N. Youssef, MD[12†]; and Palle B. Jeppesen, MD, PhD, MS[13]



Risks reported to date www.gattex.com

- Cancer: 1/109 adenocarcinoma colon (0.9%)
- GI Polyps: 14/109 (12.8%)
- GI Obstruction: 12/109 (11.0%)
- Stoma Complication: 13/53 (42%)
- Pancreatitis: 3/109 (2.7%)
- Gallbladder disease: 11/109 (10.1%)
- Fluid overload: 23/109 (21.1%; 3%CHF)
- Confusion on benzodiazepines with coma 1/109 (0.9%) - overall potential for increased drug absorption

… and now to pediatrics

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

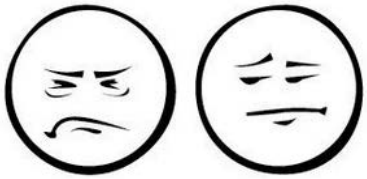
Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome

Beth A. Carter, MD[1], Valeria C. Cohran, MD, MS[2], Conrad R. Cole, MD, MPH, MSc[3], Mark R. Corkins, MD[4], Reed A. Dimmitt, MD, MSPH[5], Christopher Duggan, MD, MPH[6], Susan Hill, MRCPCH, DM[7], Simon Horslen, MB, ChB, FRCPCH[8], Joel D. Lim, MD[9], David F. Mercer, MD, PhD, FRCS(C)[10], Russell J. Merritt, MD, PhD[11], Peter F. Nichol, MD, PhD[12], Luther Sigurdsson, MD[13], Daniel H. Teitelbaum, MD[14,*], John Thompson, MD[15], Charles Vanderpool, MD[16], Juliana F. Vaughan, MD[17], Benjamin Li, MS[18,†], Nader N. Youssef, MD[19,‡], Robert S. Venick, MD[20], and Samuel A. Kocoshis, MD[3]

2017;181:102-110

First reported phase 3 study children

Although more correctly a phase 2 study = dose finding and safety monitoring in a small number of short gut patients



GI related adverse events

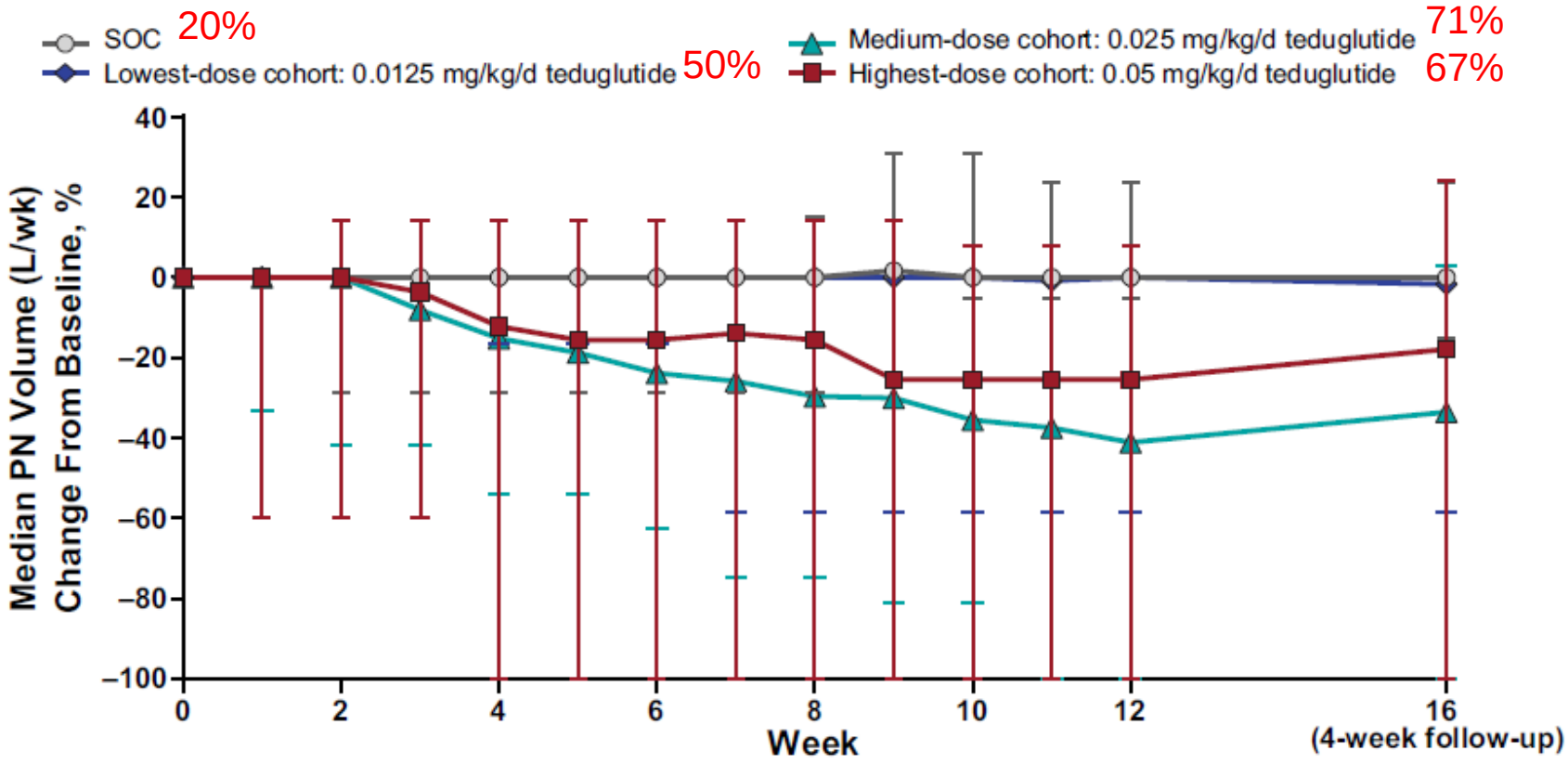


Table VI. Characteristics of patients weaned from PN/intravenous fluids

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Cohort, teduglutide mg/kg/d	Medium dose, 0.025	Highest dose, 0.05	Highest dose, 0.05	Highest dose, 0.05
Age, y	14	8	6	14
Sex	Male	Female	Male	Male
Etiology	Gastroschisis	Intestinal atresia	Hirschsprung disease	Midgut volvulus
Remaining small bowel length, cm	145	23	51	0
Stoma present (stoma type, if applicable)	No	No	Yes (ileostomy)	No
Colon remaining, %	100	100	0	100
Time since last surgical resection, y	1.0	8.4	4.3	12.2
Remaining anatomy determined by	Surgery or operative report/parental history	Surgery or operative report	Surgery or operative report	Surgery or operative report
GI symptoms				
Abnormal or irregular bowel movements	Moderate	None	None	None
Diarrhea, loose	Moderate	Mild	Severe	None
Gas, bloating	Mild	None	None	None
Heartburn, reflux, spit up	None	None	None	Mild
Nausea, feeling queasy	Moderate	None	None	None
Vomiting	Moderate	None	None	None
Teduglutide exposure at weaning, wk	10.7	4.1	12.1	8.1
Time on PN at baseline, y	1.3	8.3	6.7	12.2
Prescribed PN volume at screening, L/wk	6.9	4	9.5	11
Prescribed PN calorie at screening, kcal/wk	6747	3788	6701	4767
Prescribed number of days per week of PN at screening	7	4	7	5
Time on EN at baseline, y	14.3	N/A	N/A	N/A
Prescribed EN volume at screening, L/wk	10.1	N/A	N/A	N/A
Prescribed EN calorie at screening, kcal/wk	6720	N/A	N/A	N/A
Hours per day feeding tube used	24	N/A	N/A	N/A
Change in actual EN volume at week 12, L/wk (%)	8.4 (82.9)	N/A	N/A	N/A
Resumed PN after teduglutide discontinuation	No	No	Yes	Yes

N/A, not applicable (ie, patient did not receive EN).

24 week phase 3 study

Original Communication

Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study

Samuel A. Kocoshis, MD[1]; Russell J. Merritt, MD, PhD[2]; Susan Hill, MD[3]; Susan Protheroe, MD[4]; Beth A. Carter, MD[5]; Simon Horslen, MB, ChB[6]; Simin Hu, PhD[7]; Stuart S. Kaufman, MD[8]; David F. Mercer, MD, PhD[9]; Mikko P. Pakarinen, MD, PhD[10]; Robert S. Venick, MD[11]; Paul W. Wales, MD[12]; and Andrew A. Grimm, MD, PhD[13]

Journal of Parenteral and Enteral Nutrition
Volume 00 Number 0
xxx 2019 1–11

DOI: 10.1002/jpen.1690
wileyonlinelibrary.com
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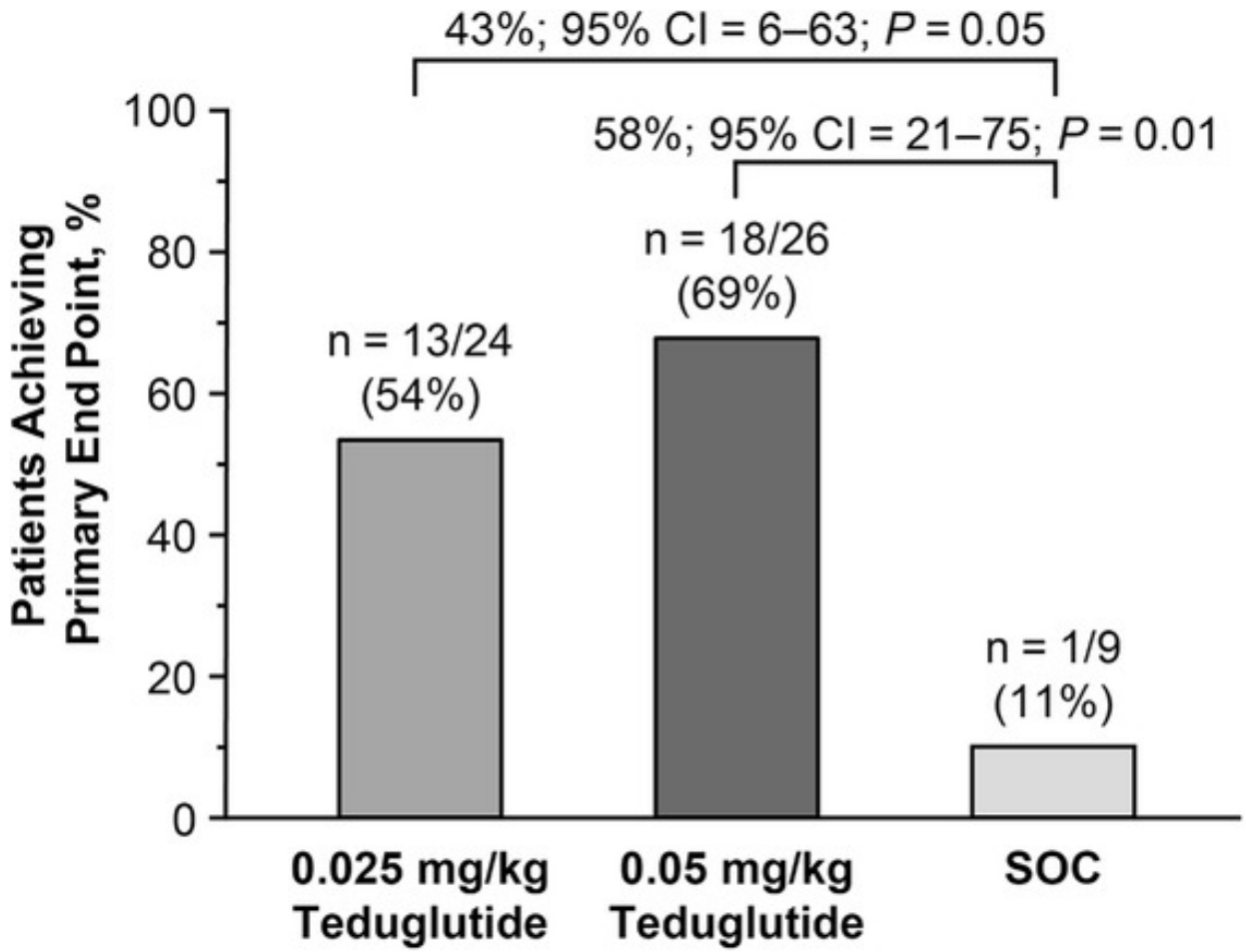
Primary endpoint:
≥20% reduction PN volume at week 24

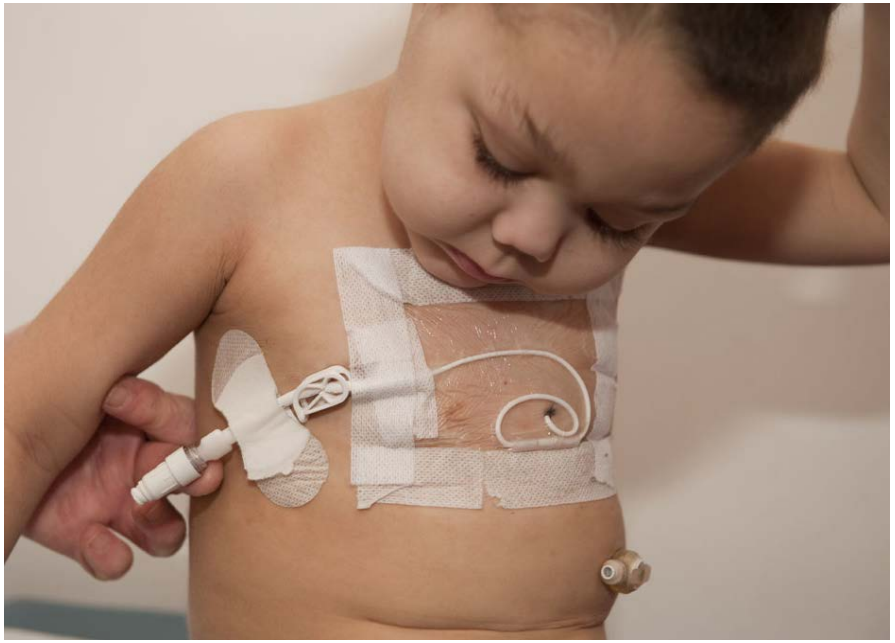
~1 day less a week
or
2-3 hours less a day



Overall autonomy

Patient	Teduglutide Dose Group	Sex, Age, Race	Underlying Diagnosis	Small Bowel Length, cm	Terminal Ileum Present, Ileocecal Valve Present (Yes/No)	% Colon Remaining in Continuity	Baseline PS Volume, mL/kg/d[a]/ Calorie, kcal/kg/d	Weeks to Attain Enteral Autonomy[b]
1	0.025 mg/kg	Female 14 y White	Midgut volvulus	122	No No	50	29/24	10
2	0.025 mg/kg	Female 14 y White	Intestinal atresia	55	No No	70	10/9	8
3	0.05 mg/kg	Female 4 y White	Gastroschisis, intestinal atresia	120	No No	Unknown	57/33	21
4	0.05 mg/kg	Female 6 y Black	Midgut volvulus	40	No No	70	57/40	21
5	0.05 mg/kg	Male 9 y White	Midgut volvulus	64	Yes Yes	90	29/14	14

Clinical Translation



Gattex®

(Teduglutide [rDNA origin]) for Injection

>300, 000$CAD 300, 000$US

Kosar et al, J Pediatr Surg 2016

Back to our patient

- Participated in 24 week trial
- EN 40% of calories
- PN x 14hrs; 7 nights [60% of calories]
- Stool output 20cc/kg/day

A glucagon like peptide 2 analogue improved his family's quality of life

Case Presentation

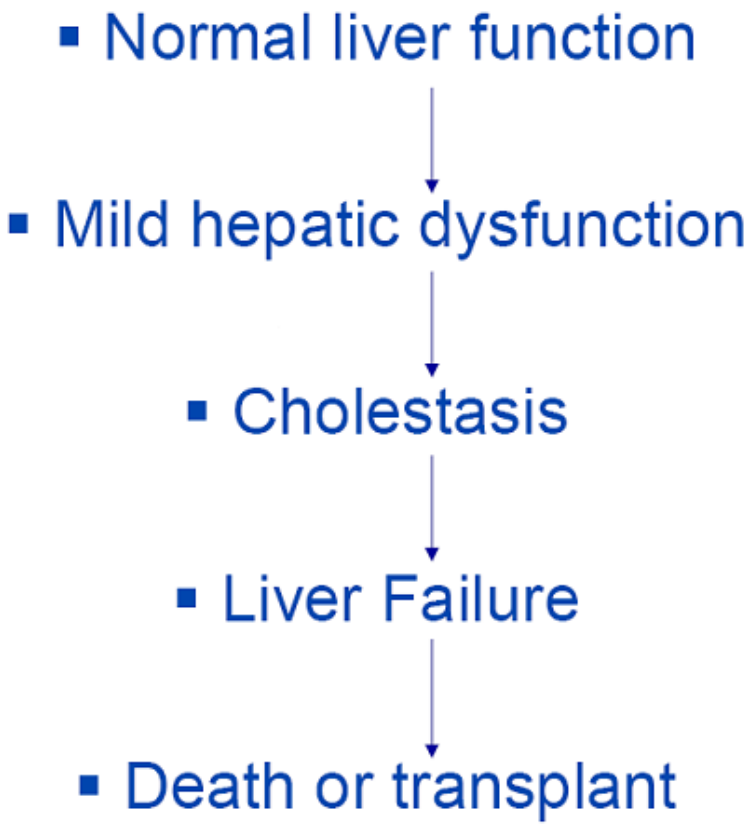
- 5mM, GA-32w, Vanishing Gastroschisis
- Anatomy post op – 30cm SB, jejunostomy, 50% colon
- While on SMOF lipids (2-2.5g/kg/d) – C. Bilirubin 90 mmol/l, total bilirubin 169, ALT 310, AST 384, GGT 163, albumin 29.
- US – increased periportal echogenicity and mild splenomegaly (8.3cm)

Diagnosis?

IFALD - Definition

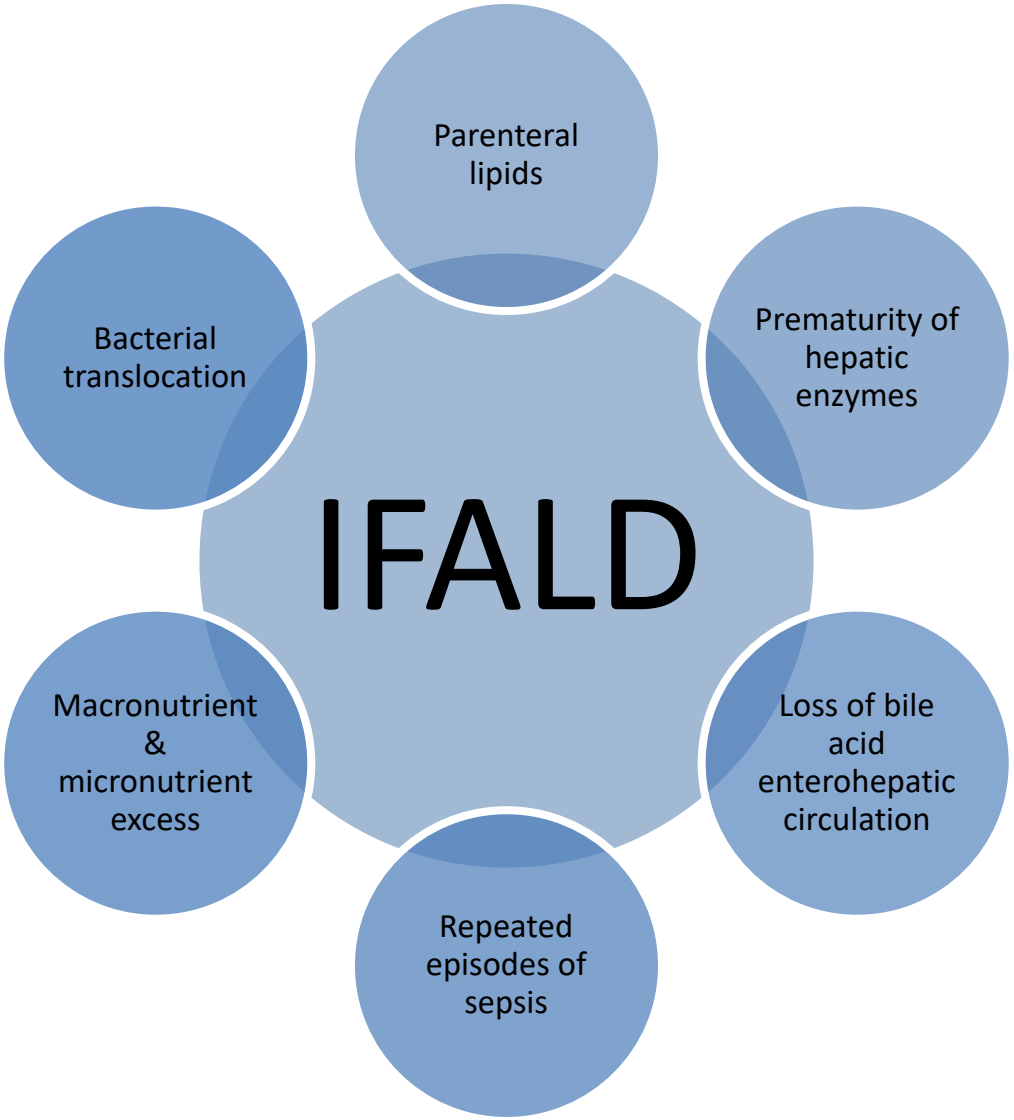
- Hepatobiliary dysfunction as a consequence of medical and surgical management strategies for intestinal failure, which can variably progress to end-stage liver disease, or can be stabilized or reversed with promotion of intestinal adaptation

- Advanced IFALD – total bilirubin persistently >100 mmol/L (>2-4 weeks)



ESPGHAN position paper; Lacaille et al. JPGN 60;272:2015

IFALD Pathogenesis



Case Presentation

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- US – increased periportal echogenicity and mild splenomegaly (8.3cm)

Treatment options?

- Creation of sigmoid colostomy – increase enteral capacity
- Prevention of sepsis
- Omegaven?
- Lipid minimization?
- Listing for transplantation?

Case Presentation

- Jejunostomy revised to sigmoid colostomy; SMOF changed to Omegaven® 1g/kg/d; enteral nutrition increased
- At 1y of age – TPN depended, 30% of nutrition is enteral, C. Bilirubin 4mmol/l, back on SMOF
- Until 3y of age – 6 CLABSI including one *candida albicans* and one PICU admission (*Streptoccocus A sepsis)*
- At 3y of age – Upper GI bleeding due to GE varices
- US – lobulated liver, coarse parenchyma, splenomegaly, GE varices
- Total bilirubin 3 mmol/l, ALT 82, AST 53, GGT 50, albumin 28, PLT 45,000 $X10^6$/l

Diagnosis?

Liver Biopsy?

- Biopsy – Dense non-inflammatory portal fibrosis, no cholestasis

Persistence of Hepatic Fibrosis - Omaha

Methods

- Six children with IF on Omegaven ®
- Liver biopsy – during an open abdominal operation / Pre-Tx evaluation
- Included: >1 biopsy taken

TABLE 1. Pathologic scoring system used in evaluation of biopsies

	0	1	2	3	4
Cholestasis	No cholestasis	≥1 Parenchymal features* but mild in extent	≥2 Parenchymal features, moderate in extent	≥3 Parenchymal features and ≥1 portal tract features†, mild to moderate in extent	≥3 Parenchymal features and ≥1 portal tract features, severe in extent
Fibrosis	Normal connective tissue	Fibrous portal expansion	Periportal fibrosis or rare portoportal septa	Fibrous septa with architectural distortion; no obvious cirrhosis	Cirrhosis
Inflammation	LPN: None	LPN: Minimal, patchy	LPN: mild; involving some or all portal tracts	LPN: moderate; involving all portal tracts	LPN: severe; may have bridging fibrosis
	LIN: None	LIN: minimal; occasional spotty necrosis	LIN: mild; little hepatocellular damage	LIN: moderate; with noticeable hepatocellular damage	LIN: severe with prominent diffuse hepatocellular damage
Steatosis	<5% fat-containing hepatocytes	5%–33% fat-containing hepatocytes	34%–66% fat-containing hepatocytes	>66% fat-containing hepatocytes	
Ductal proliferation	No ductal proliferation	Ductal proliferation present			

LIN = lobular inflammation and necrosis; LPN = lymphocytic piecemeal necrosis.
*Parenchymal features: hepatocellular bile pigment; canalicular bile plugs, Kupffer cell bile pigment, zone 3 hepatocyte swelling/degeneration.
†Portal tract features: bile ductular proliferation; inspissated bile in bile ductules; inspissated bile in bile ducts.

Results – Liver

TABLE 3. Summary of clinical, laboratory and pathological data for 6 study subjects

	1				2		3				4		5			6	
Age at biopsy, wk	43	52	99	131	14	41	8	34	40	67	8	38	11	19	47	28	83
Length, cm	67.5	73	80.5	84.5	50.5	65	54.6	69	71	77.5	46	63	58.5	62	73.5	62	75
Weight, kg	8.2	9.5	10.8	12	4.1	8.3	4.1	7.2	8.3	9.7	2.4	7.2	4.9	6.6	9	6.6	9.4
% Enteral	15	0	0	16	0	70	0	0	15	47	0	25	30	35	35	94	86
% Parenteral	85	100	100	84	100	30	100	100	85	53	100	75	70	65	65	6	14
Total bili, mg/dL	0.4	1.7	0.4	0.4	3.4	0.4	6.5	0.4	0.3	0.3	17.4	0.6	4.4	0.3	0.4	0.4	0.7
Direct bili, mg/dL	0.2	0.2	0.1	ND	ND	0.1	3.6	ND	ND	ND	10.4	ND	3.6	ND	ND	0.1	ND
AST, U/L	75	107	95	39	58	56	142	28	53	27	52	83	105	94	129	36	70
ALT, U/L	125	127	201	121	77	42	109	21	75	22	29	141	129	231	229	44	116
GGT, U/L	196	96	31	35	107	23	ND	22	18	32	223	ND	139	159	122	20	44
Alk phos, U/L	185	231	260	164	548	271	475	251	257	310	673	348	510	385	557	401	251
Trig, mg/dL	60	40	ND	17	59	53	96	41	28	50	90	37	67	34	ND	29	26
Platelets	275	247	225	212	397	325	241	204	194	272	101	118	422	247	241	273	454
PT-INR	1.6	1.2	1.2	1.1	1.2	1.2	ND	1.2	1.1	1.1	102	1.1	1	1.2	0.9	1.4	1.2
Albumin	2.3	2.9	3.2	3.2	3.6	2.1	2.3	1.8	3.5	2.3	2.6	3.1	3	2.5	3.3	3.1	3.1
Time on FOE at biopsy, wk	11	20	Off	Off	6	Off	1	27	33	Off	1	31	0	9	36	20	75
Steatosis	1	0	1	1	0	0	0	1	0	0	0	1	0	0	0	0	1
Cholestasis	1	1	0	0	2	0	3	1	1	0	4	1	3	2	0	1	0
Inflammation	0–1	1–2	0	0	0–1	0–1	2	1	1	1	1	0–1	1	0	0	2	0
Fibrosis	3	3	3	3	2	2	0	2	3	3	1	2	1	2	2	2	1
Ductal proliferation	No	Yes	No	No	No	No	No	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No

- Total bilirubin levels normalized after a median of 6 weeks.
- Cholestasis and inflammation scores improved in all to normal – mildly abnormal
- Fibrosis scores stable or rose in 5/6 patients (score of 2-3)
- No overt PHT findings or synthetic dysfunction

Journal of Pediatric Surgery xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Persistence of hepatic fibrosis in pediatric intestinal failure patients treated with intravenous fish oil lipid emulsion

Christina Belza [a], Rory Thompson [b], Gino R. Somers [b], Nicole de Silva [a], Kevin Fitzgerald [c], Karen Steinberg [a], Glenda Courtney-Martin [a], Paul W. Wales [a,c], Yaron Avitzur [a,d,*]

Persistence of Hepatic Fibrosis - Toronto

Methods

- Six children with IF on fish oil based emulsions (Omegaven ® / SMOF ®)
- Liver biopsy – during an open abdominal operation
- Included: >1 biopsy taken

Demographics				Anatomy				
ID	**Gender**	**Gestational Age (weeks)**	**Diagnosis**	**SB Length (cm)***	**%SB for age ****	**LB length (cm)***	**%LB for age ****	**ICV**
1	M	40	Hirschsprung's Disease	30	20	0	0	No
2	M	34	Jejunal atresia	45	25	0	100	No
3	M	40	Volvulus	129	28	60	50	No
4	M	35	Gastroschisis	10	5	25	50	No
5	M	32	Gastroschisis	18	13	15	50	No
6	M	34	Gastroschisis	21	15	16	45	No
MED		**35.83**		**42.17**	**17.7**	**19.4**	**24.4**	

Belza et al. J Ped Surg 52;795: 2017

Liver Pathology Scores

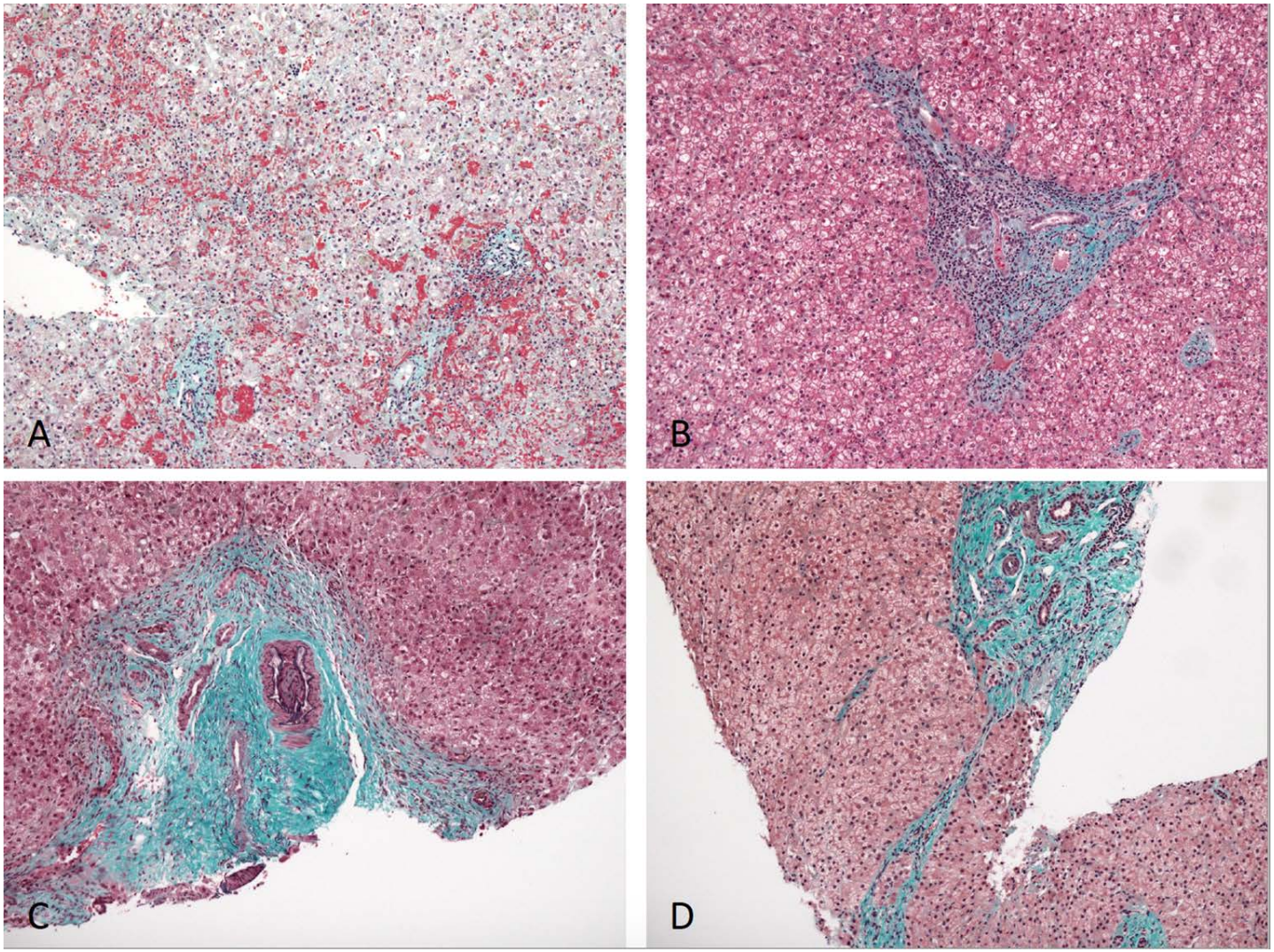
Median time between biopsies – 858 days (range 478-1663)

	ISHAK STAGE			KNODELL SCORE			CHOLESTASIS		
ID	Initial	Follow-up	Change	Initial	Follow-up	Change	Initial	Follow-up	Change
1	3	2	↓	7	2	↓	3	2	↓
2	1	3	↑	4	2	↓	3	2	↓
3	4	3	↓	7	5	↓	3	2	↓
4	4	3	↓	7	2	↓	4	2	↓
5	3	5	↑	3	2	↓	4	2	↓
6	3	3	o	3	3	o	4	1	↓
Med	3	3		5.5	2		3.5	2	

3/6 patients - no change or worsening in the fibrosis score

Belza et al. J Ped Surg 52;795: 2017

Liver Pathology



Belza et al. J Ped Surg 52;795: 2017

Patient Outcome

ID	Age at last Follow up (years)	Omegaven (months)	Enteral Autonomy	Sepsis per 1000/catheter days	Listed for Transplant	Transplant Indication	Outcome
1	8.5	67.6	40%	5.0	Yes	Liver failure	Liver & intestine transplant
2	6.5	3.1	100%	22.6	No		Alive
3	9.6	30.2	60%	1.3	No		Alive
4	7.7	67.3	23%	1.7	No		Alive
5	3.9	17.6	58%	9.3	Yes	Portal hypertension with recurrent GI bleeding	Listed for liver & intestine transplant
6	2.9	13.9	48%	1.0	No		Alive
Median	7.1	23.9	51%	3.35			

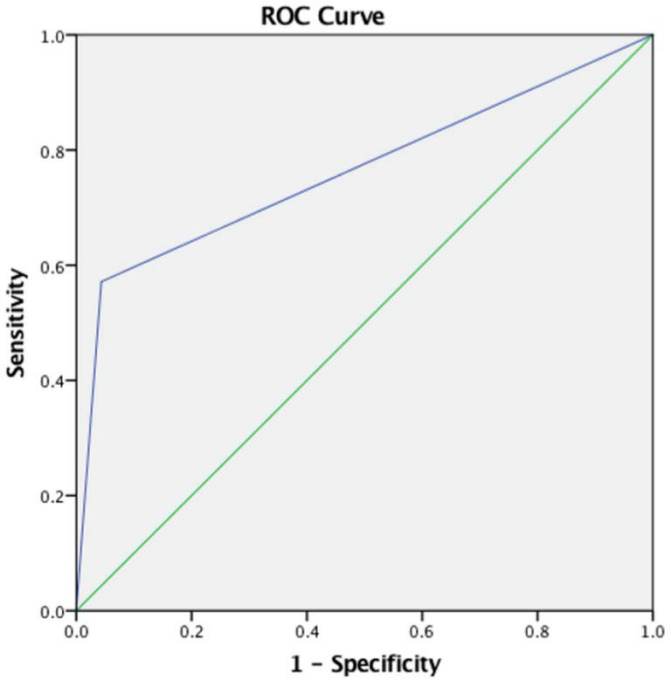
- Two (7%) patients out of the original cohort of 29 responders required transplant

Belza et al. J Ped Surg 52;795: 2017

Diagnosis of Fibrosis Transients Elastography

- 30 patients with a routine liver biopsy during surgery

Fibrosis Level	Probability	Sensitivity	Specificity	PPV	NPV	C-Statistic
Low (0-2)	22/25	95.7%	57.1%	88.0%	80.0%	0.764
High (3-4)	4/5	57.1%	95.7%	80.0%	88.0%	



Belza et al. CIRTA 2019; Paris

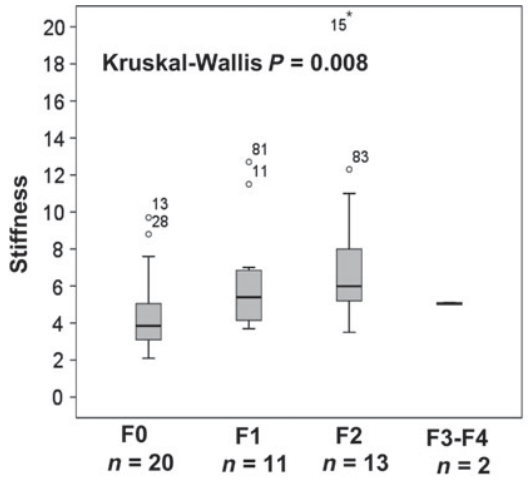
Diagnosis of Fibrosis Transients Elastography

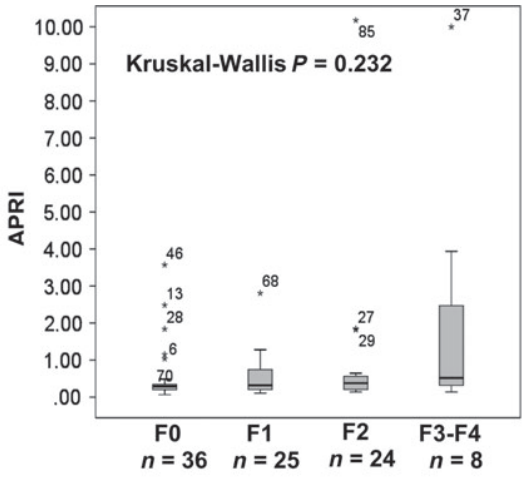
- 93 biopsies from 57 children with IF
- TE – 46 children

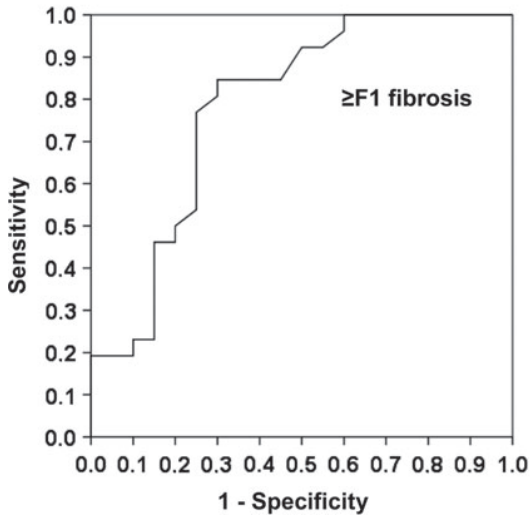
- Fibrosis – 61%
- Metavir stage:
  F1 - 27%
  F2 – 26%
  F3/4 – 9%

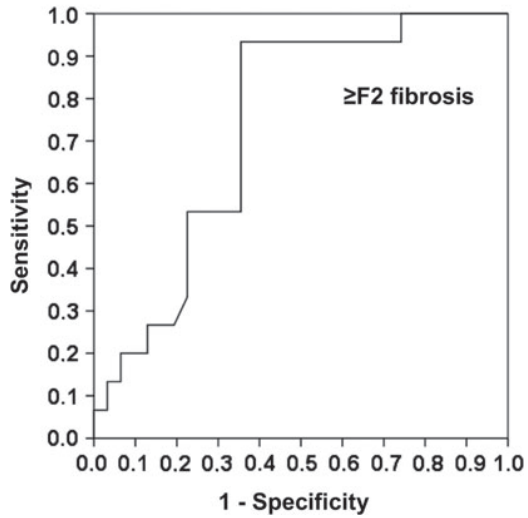
- ≥F1 – R stat – 0.78
- ≥F2 – R stat – 0.73

- AST to PLT ratio (APRI) – not correlated with fibrosis









Hukkinen et al. Liver Int 36;361: 2016

Case Presentation

- In the following 6m – signs of portal hypertension
- Repeated GE variceal banding, another episode of upper GI bleeding
- INR 1.5

Treatment?

- Listed for liver –intestine transplantation
- Transplanted at 6y of age
- Now 1y post transplant – doing well, off PN

Pediatric Listing Criteria - 2019

Criteria for placement on a wait list for intestinal transplantation

- Evidence of advanced or progressive intestinal failure-associated liver disease
  - *Hyperbilirubinemia >75 micromol/L[2] (4.5 mg/dL) despite intravenous lipid modification strategies that persists for more than 2 months*
  - Any combination of elevated serum bilirubin, reduced synthetic function (sub-normal albumin or elevated INR), and laboratory indications of portal hypertension and hypersplenism
- *Thrombosis of three out of four discrete upper body central veins or occlusion of a brachiocephalic vein*
- *Life-threatening morbidity in the setting of indefinite parenteral nutrition dependence as suggested by:*
  - *2 admissions to an intensive care unit (after initial recovery from the event resulting in intestinal failure) because of cardio-respiratory failure (mechanical ventilation or inotrope infusion) due to sepsis or other complications of intestinal failure*
- Invasive intra-abdominal desmoids in adolescents and adults
- Acute diffuse intestinal infarction with hepatic failure
- Failure of first intestinal transplant

Kaufman, Avitzur et al. Transplantation 2019