Published in final edited form as:
J Pediatr Surg. 2013 January ; 48(1): 228–232. doi:10.1016/j.jpedsurg.2012.10.044.

Short-Term Intravenous Fish Oil and Pediatric Intestinal Failure Associated Liver Disease: 3-year Follow-up on Liver Function and Nutrition

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Abstract

Intravenous fish oil (FO) has changed the management of intestinal failure associated liver disease (IFALD). This report describes two IFALD patients who received FO for 5 and 10 months, respectively and reports on their 3-year follow-up.

Keywords

cholestasis; parenteral nutrition; fish oil; soybean oil; short bowel syndrome; premature

The authors have no conflicts of interest to disclose.

Introduction

Intestinal failure (IF) is the gastrointestinal tract's inability to absorb adequate fluids and nutrients. This condition results in parenteral nutrition (PN) dependence. While PN is life-sustaining, it can be associated with intestinal failure associated liver disease (IFALD) – a complication that can result in liver failure and the need for transplant. Risk factors for IFALD include prematurity, lack of enteral nutrition (EN), duration of PN, sepsis, and multiple gastrointestinal surgeries. Studies have demonstrated that when standard intravenous soybean oil (SO) is replaced with fish oil (FO) (Omegaven®, Fresenius Kabi, Bad Hamburg, Germany), direct hyperbilirubinemia is more likely to resolve[1-10].

FO, which is not approved by the United States Food and Drug Administration (FDA), is only available under compassionate use and research protocols in the United States, and costs significantly more than SO. Because third party payers do not always reimburse for experimental therapies, hospitals and investigators shoulder the majority of the expense. Adding to the cost, investigators may continue FO until PN discontinuation even if direct hyperbilirubinemia has resolved. To date, the longest median follow-up on liver function reported on children who have received FO is 16 months[9]. There is no data on patients whose FO has been discontinued prior to intestinal adaptation, and limited follow-up on subjects after adaptation[2-10].

We present two children who received FO for IFALD. FO emergency use was granted by the FDA, and informed consent was obtained. In order to limit potential toxicities associated with FO and the overall financial cost of the drug, the decision to terminate FO was made by a multi-disciplinary team taking into account risk factors for IFALD and after reversal of cholestasis and EN improvement. To our knowledge, this report provides the longest follow-up to date on children who have received an exclusively FO-based lipid emulsion, and is the only report on children whose FO was discontinued despite the need for ongoing PN.

Case 1

Case 1 is a full-term neonate with gastroschisis and intrauterine growth restriction (birth weight 1.7 kg). A silo was placed, and on day of life (DOL) 2, she developed necrotic bowel requiring resection of her ileocecal valve and all but 15 cm of small bowel. Abdominal closure occurred on DOL 5. Because of anticipated adhesions and multiple abdominal surgeries, a jejunocolostomy was created on DOL 56. Advancement of EN was initially limited by gut dysmotility and short gut. By age 2 months, she developed biochemical IFALD (Figure 1). Her platelet count and coagulation profile, however, were normal. At age 3 months, in an effort to avoid transplant, the patient's SO was replaced with FO (1 gm/kg/d) (EIND 104,766). Prior to transitioning to FO, Case 1 was receiving 121 kcal/kg/d and 3 gm/kg/d of SO (Table 1). By week 24 after FO initiation, her serum direct bilirubin concentration was normal (< 0.2 mg/dL on 2 consecutive measurements separated by 1 week). Her serum transaminase concentrations normalized by week 29 (Figure 1). After 10 months of treatment, when FO was discontinued, 14% of her calories were from EN, and her growth remained suboptimal (Table 2).

At 3.3 years of age, 3 years after FO initiation (27 months after FO discontinuation), she continues to receive the majority of her calories from PN and 2 gm/kg/d of SO. While her serum bilirubin concentrations, platelet counts, and international ratios are normal, her serum transaminase concentrations occasionally fluctuate above normal (Figure 1). She has demonstrated adequate “catch-up” growth, but her linear growth remains below average (Table 2). No adverse events including bleeding or an essential fatty acid deficiency were associated with FO.

Case 2

Case 2 is an ex-36 week neonate with a birth weight appropriate for gestational age and jejunal atresia with an apple-peel like deformity. On DOL 3, the atresia was repaired with primary anastomosis. Multiple intestinal strictures later developed requiring small bowel resection on DOL 51, leaving her with a partial duodenum, 10 cm of ileum, ileocecal valve, and a full colon in continuity. At 1 month of age, Case 2 developed a direct hyperbilirubinemia, and by 6 months of age she demonstrated severe IFALD manifested by cholestasis, abnormal serum transaminase concentrations, a mild thrombocytopenia, and a liver biopsy demonstrating bridging fibrosis (Figure 1). 2 months prior to the FO start date, Case 2's platelet count ranged from 97,000-130,000. At age 6.5 months, her SO (2 gm/kg once a week) was replaced with FO (1 gm/kg/d), and she received five months of therapy (EIND 104,951). Prior to FO, she was receiving 129 kcal/kg/d and 46% of her caloric intake was from EN (Table 1). While her cholestasis resolved by week 17, her serum aspartate and alanine aminotransferase concentrations corrected after FO discontinuation, by week 28 and 41, respectively (Figure 1). 1 year after FO discontinuation, her platelet count was persistently above 150,000. When FO was terminated, she was placed on PN without SO as she was receiving 70% of her calories from EN.

At 2.4 years of age, almost 2 years after starting FO, Case 2 demonstrated complete intestinal adaptation. At 3.5 years of age, 3 years after FO initiation (2.5 years after FO discontinuation), her liver function tests are normal and her growth is acceptable (Figure 1, Table 2). No adverse events were associated with FO.

Discussion

We present two children with short bowel and IFALD in whom FO served as a means to reverse biochemical IFALD. Case 1 and 2's resolution of direct hyperbilirubinemia, strictly defined as a direct bilirubin < 0.2 mg/dL on 2 consecutive measurements at least 1 week apart, occurred at FO weeks 24 and 17, respectively. Using this information and data from two published studies, we implemented a research protocol (IND 105,326) providing 24 weeks of FO to children at high risk for the complications of IFALD[3,4]. In the study published by Gura et al the median time to achieve a direct bilirubin < 2 mg/dL was 9.4 weeks for patients with congenital or acquired gastrointestinal disorders with a mean age of 14 weeks and median baseline direct bilirubin of 5.4 mg/dL [4]. Subjects received 1 gm/kg/d of FO. In comparison, Diamond et al provided a combination of FO and SO, each dosed at 1 gm/kg/d, to older patients (median age 7.5 months) with more severe cholestasis (median conjugated bilirubin 8.06 mg/dL). 9 out 12 patients demonstrated resolution of cholestasis, defined as a conjugated direct bilirubin of 0 μmol/L, at a median time of 24 weeks. Interestingly, 5 patients were transitioned to FO monotherapy due to lack of response.[3]

Case 1 is unique—unlike Case 2 and most IFALD patients who receive FO in the United States, Case 1's FO was terminated prior to PN discontinuation. Case 1 maintained normal serum bilirubin concentrations despite ongoing PN, septic episodes, and SO reinitiation. To our knowledge, this is the first report of FO termination and SO reinitation in a patient with extreme SBS and IFALD who has not redeveloped cholestasis. Case 2, on the other hand, maintained normal serum bilirubins and liver functions tests off FO, but did not restart SO because she was receiving sufficient enteral calories (Table 1). A concern is that once FO is terminated, IFALD will return. In comparison to younger children, older children have a decreased risk of IFALD. Hence, FO initiation at an earlier age and prior to advanced IFALD may be advantageous. Once two milestones have been achieved—biochemical resolution of IFALD and EN progress, the liver may be less susceptible to SO and PN toxicities and restarting SO at an older age may be acceptable. Even though FO is more

expensive than SO, considering the cost of a transplant and post-transplant care, FO may be a more economically sound alternative to SO[12].

Despite more advanced liver disease and initiation of FO at an older age, Case 2 experienced reversal of cholestasis in a shorter time frame than Case 1 (Figure 1). Because FO was not available at our institution until March 2009, Case 2's FO start date was delayed. Explanations for Case 2's quicker reversal are a more appropriate gestational age, more favorable gastrointestinal anatomy, greater enteral intake, enhanced intestinal adaptation, and fewer septic episodes[13,14] (Table 1). In both cases, serum bilirubin concentrations normalized before transaminase concentrations as seen in prior reports, and Case 2's transaminases normalized after FO[2-4] (Figure 1).

It remains unclear if FO can reverse advanced hepatic histological changes and portal hypertension in the pediatric population[15]. Case 2 had evidence of portal hypertension at FO initiation and discontinuation as evidenced by clinical exam, liver function tests, and a mild thrombocytopenia (Figure 1). While ultrasounds with doppler would have provided additional information, they were not performed. We can only speculate if longer FO administration would have resulted in a more rapid resolution of Case 2's transaminitis and thrombocytopenia, or if Case 1 would have less fluctuations in her transaminases. Previous reports have demonstrated improved median platelet counts and no change in International Ratios with FO[2-4]. In the absence of a repeat liver biopsy, it is unknown if Case 2's liver fibrosis may have improved[15].

The mechanism by which FO reverses IFALD is likely related to a lower dose of fat (1 gm/kg/d), lack of phytosterols, the anti-inflammatory properties of omega-3 fatty acids and a higher dose of the antioxidant Vitamin E in the form α-tocopherol. SO is dosed up to 4 gm/kg/d and contains high concentrations of phytosterols and inflammatory omega-6 fatty acids, and a lower dose of Vitamin E in the form of γ-tocopherol. Phytosterols reduce biliary flow by antagonizing the farnesoid X receptor, a bile acid nuclear receptor[16]. Compared to γ-tocopherol, α-tocopherol is more efficient at counteracting free radical damage from lipid perioxidation[10]. While a change in the composition of the lipid emulsion may be responsible for the resolution of cholestasis, improvement in serum bilirubin concentrations has been noted with SO dose reduction[17,18]. In attempt to limit her exposure to the hepatoxic effects of SO, Case 2 was prescribed a minimal amount of SO (Table 1). Despite this approach, her IFALD progressed. It remains unclear how lipid composition and dose interact, and which one is more important.

Lipid sparing has raised concerns as premature and IF patients are at high risk for failure-to-thrive and essential fatty deficiencies. While some studies of IFALD children have demonstrated adequate growth with lipid minimization, larger, long-term studies are lacking[4,17]. While Case 1's growth was suboptimal prior to and during FO, she demonstrated adequate “catch-up” growth with 2 gm/kg/d of SO and improved enteral intake (Table 1). Case 1's persistently negative z-score for length is mostly a reflection of her intestinal failure, genetic potential and history of intrauterine growth restriction[14]. In contrast, Case 2 demonstrated adequate growth despite lipid sparing during her PN course. In both cases, improved growth is most likely related to improved enteral absorption and, for Case 1, an increase in the dose of her intravenous fat emulsion.

While FO dosed at 1 gm/kg/d has generally not been associated with an essential fatty acid deficiency, less than 1 gm/kg/d of FO or SO can cause a deficiency[4,17,19,20]. Term neonates require 0.1 gm/kg/d and preterm neonates require 0.25 gm/kg/d of SO to prevent an essential fatty acid deficiency[20]. Despite 2 gm/kg once a week of SO, standard laboratory evaluations

revealed an appropriate triene-tetraene ratio (0.028) for Case 2. This is most likely because she was receiving a fair amount of enteral nutrition in the form of breast milk.

FO provided a bridge to bowel adaptation for Case 2. While children with extreme short gut have been weaned from PN, Case 1 may ultimately require a combined small bowel-liver transplant or isolated small bowel transplant. Her risk factors include poor gastrointestinal anatomy and function necessitating long-term PN, and history of septic episodes and central venous catheter replacements. However, her overall mortality has improved. Until data is available from follow-up and randomized controlled studies, FO's effect on long-term transplant-free survival is unknown. While a randomized controlled trial in a population with advanced IFALD is controversial, this type of trial could provide information on FO and SO minimization efficacy and safety, along with guidelines for FO candidacy and duration. In summary, this report suggests that a limited FO course may help reverse biochemical IFALD. Using FO as a bridge to intestinal rehabilitation or therapy to reverse IFALD so that SO can be restarted at a later date when the liver has matured and can be further protected by EN may be safe and cost-effective.

Acknowledgments

Funding

Kara Calkins, MD has received funding from the NIH K12HD00140, MO1 RR000865, and 2T32GM075776. Stephen Shew, MD has received funding from the NIH K08HD052885. Robert Venick, MD has received funding from the Today's and Tomorrow's Children Fund, University of California, Los Angeles. Intravenous fish oil (Omegaven®, Fresenius Kabi, Bad Hamburg, Germany) was purchased with funds from James Yoo, MD, the Division of Pediatric Surgery, and the Woman's Auxiliary Fund (University of California, Los Angeles).

Abbreviations

IF	intestinal failure
PN	parenteral nutrition
IFALD	intestinal failure associated liver disease
EN	enteral nutrition
SO	soybean oil
FO	fish oil
FDA	Food and Drug Administration
DOL	day of life

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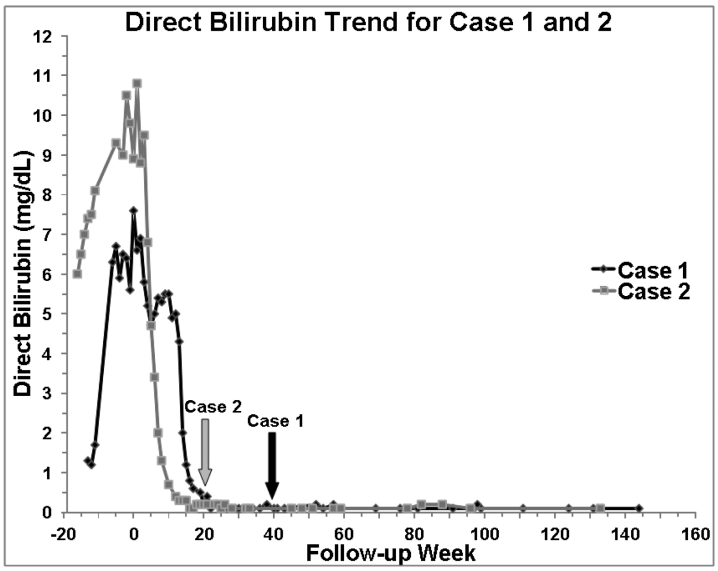
A.



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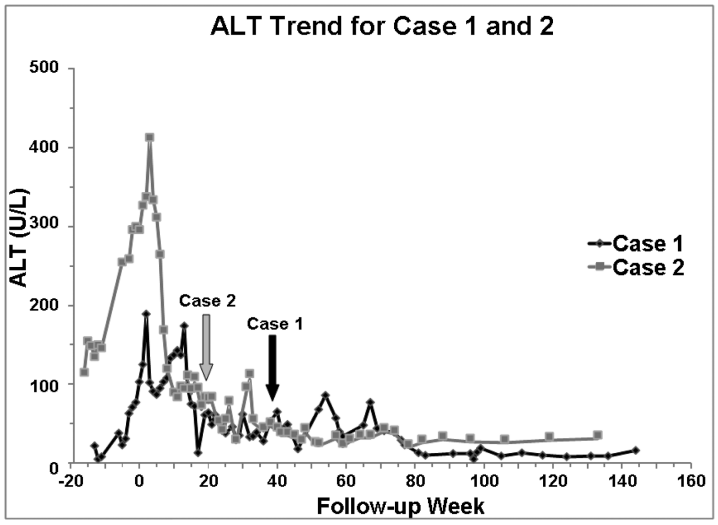

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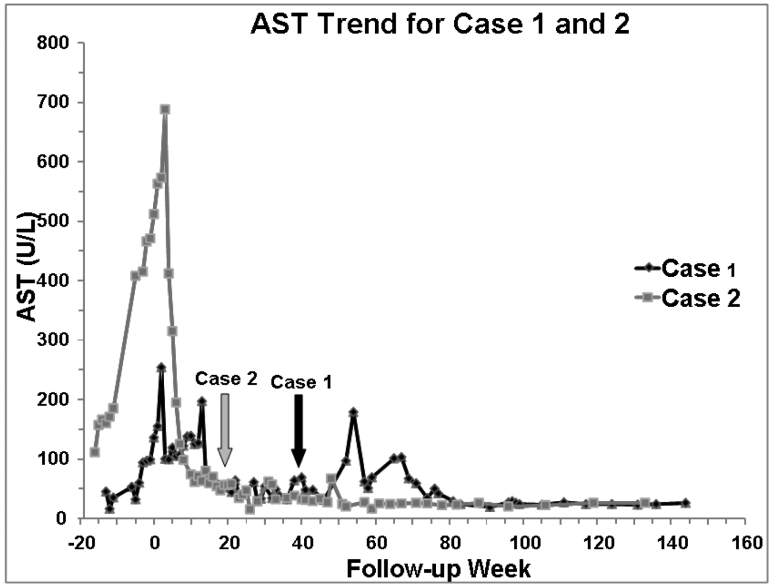

Figure 1.

A. Direct bilirubin trend, **B.** Alanine aminotransferase (ALT) trend, and **C.** Asparate aminotransferase (AST) trend for Case 1 and 2. Week 0 represents baseline, when FO (fish oil) was started. Arrows indicate FO discontinuation. A normal direct bilirubin was defined as < 0.2 mg/dL on 2 consecutive measurements. A normal ALT and AST were defined as ≤45 and 36 U/L, respectively on 2 consecutive measurements.

Table 1
Factors Affecting Intestinal Failure Associated Liver Disease in Each Case

Nutrition and other confounders of intestinal failure associated liver disease at the start of fish oil (FO), FO discontinuation, and 3-year follow-up for Case 1 and 2.

	Case 1	Case 2
Baseline		
PN Calories (kcal/kg/day)	121	70
Glucose Delivery Rate (mg/kg/min)	22	16
Amino Acids (gm/kg/d)	3.5	1.4
Soybean Oil	3 gm/kg/day	2 gm/kg once a week
Type of EN	None	Breast milk plus rice cereal
EN Calories (kcal/kg/day)	0	59
Total Calories (kcal/kg/d)	121	129+
Number of Gastrointestinal Surgeries†	4	2
Number of Septic Episodes‡	0	0
At FO Discontinuation		
PN Calories (kcal/kg/day)	90	29
Glucose Delivery Rate (mg/kg/min)	23	3
Amino acids (gm/kg/d)	2.6	1.2
FO (gm/kg/day)	1	1
Type of EN	Puree food plus 340mL ½ strength elemental infant formula	Puree food plus 780mL elemental pediatric formula
EN Calories (kcal/kg/day)	17+	70+
Total Calories (kcal/kg/d)	107+	99+
Number of Gastrointestinal Surgeries†	0	0
Number of Septic Episodes during FO‡	4	1
3-year Follow-up		
PN Calories (kcal/kg/day)	83	0
Glucose Delivery Rate (mg/kg/min)	23	0
Amino Acids (gm/kg/d)	3.5	0
Soybean Oil (gm/kg/day)	2	0
Type of EN	Pediatric diet Ad Lib	Pediatric diet plus 625mL elemental pediatric formula
EN Calories (kcal/kg/day)	Variable	46+
Total Calories (kcal/kg/d)	83+	46+
Number of Gastrointestinal Surgeries†	0	0
Number of Septic Episodes after FO‡	2	3

†Gastrointestinal surgeries do not include gastrostomy tube placement.

‡Sepsis is defined as a positive blood culture with symptoms suggestive of sepsis and need for intravenous antibiotics.

Table 2

Growth for Case 1 and 2.

	Case 1	Case 2
Baseline		
Weight (Z-score) *	-2	-0.3
Length (Z-score) *	-2.8	0
At FO Discontinuation		
Weight (Z-score) *	-1.9	-0.7
Length (Z-score) *	-1.5	-1.1
3-year Follow-up		
Weight (Z-score) *	0	-0.5
Length (Z-score) *	-2	-0.5

* Z-scores calculated using information from the Center for Disease Control data tables on infant weight- and length-for-age[11].