Infants

Use of Fish Oil-Based Lipid Emulsions in Infants With Intestinal Failure-Associated Liver Disease: A Case Series

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Abstract: *The use of fish oil–based lipid emulsions (FOLE) in the treatment of intestinal failure–associated liver disease (IFALD) remains investigational. Additional evidence for safety and efficacy, particularly in the neonatal and pediatric populations, is needed. Retrospective chart review was conducted on 10 infants with short bowel syndrome who received FOLE for IFALD. Direct bilirubin concentrations normalized in surviving subjects within 4.1 to 22.7 weeks of starting treatment. Although earlier initiation of FOLE was not associated with more rapid normalization of direct bilirubin concentrations, it trended toward a significant correlation with reduced length of hospital stay (P = .058). The reduction in direct bilirubin levels and transition from parenteral to enteral feeding were statistically significant within 6 weeks of initiating the FOLE. Subjects did not have impaired growth and did not develop an essential fatty acid deficiency. These infants were discharged from the hospital 7.9 to 42.3 weeks after starting FOLE treatment, and 2 infants had transitioned completely off parenteral nutrition at discharge. In this study, FOLE appeared to be a safe and effective treatment for IFALD in infants with short bowel syndrome. Future studies are necessary to determine whether FOLE can help to prevent or shorten the duration of cholestasis.*

Keywords: hepatology/liver diseases; intravenous fish oil-based lipid emulsion; infant; early lifespan nutrition; newborn or neonate; gastrointestinal disorders; enteral and parenteral feeding; nutrition support/special diets

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Background

Intestinal failure–associated liver disease (IFALD) is a common disorder in parenteral nutrition (PN)–dependent infants with short bowel syndrome and can result in potentially life-threatening liver cirrhosis if untreated.[1-3] Although the cause of IFALD is not completely understood, the high ratio of ω-6 to ω-3 fatty acids and the phytosterol content of conventional vegetable oil–based lipid emulsions are thought to be contributing factors.[4-6] Restricting intravenous lipid infusion may help to prevent or treat IFALD; however, this practice can be problematic because lipids are thought to be an important source of nonprotein calories and essential fatty acids.[7] In a landmark case report by Gura et al,[8] 2 infants with intestinal failure and severe IFALD were provided Omegaven (Fresenius Kabi, AG, Bad Homburg, Germany), an intravenous fish oil–based lipid emulsion (FOLE) that is

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phytosterol-free and rich in long-chain ω-3 fatty acids. These infants had reversal of their cholestasis and improvement in hepatic function as evidenced by normalization of direct bilirubin and aminotransferase concentrations.[8] These and other findings prompted the US Food and Drug Administration (FDA) to permit the compassionate use of Omegaven in infants with IFALD who have not responded to conventional therapies.

Since this time, several case reports,[9-15] case series,[16-18] and case-control studies[19-21] have reported resolution of cholestasis in IFALD patients receiving Omegaven. However, there is a need for additional evidence regarding FOLE administration in the neonatal and pediatric populations, as currently available reports generally focus on a limited number of outcomes apart from cholestasis. A recent systematic review concluded that additional studies with long-term, clinically relevant outcomes are needed.[22] In this case series, we provide a detailed evaluation of our experience with FOLE administration in 10 infants with short bowel syndrome and IFALD.

Methods

Patients and Treatment Protocol

Since December 2009, patients with IFALD were provided with Omegaven in accordance with an FDA open-label protocol. The conventional lipid emulsion at this facility is soybean oil–based Intralipid (Fresenius Kabi, AG, Bad Homburg, Germany). Under the open-label protocol, infants with short bowel syndrome who are PN-dependent and weigh at least 3 kg are eligible to receive FOLE at 1 g/kg/d if they have 2 consecutive direct bilirubin levels 2.0 mg/dL or greater, indicative of IFALD, and are thought to be at risk for significant hepatic injury due to prolonged need for PN (>30 days). Short bowel syndrome was defined as an anatomically shortened small intestine or functional short bowel syndrome with intestinal failure, defined as intestinal malabsorption due to a primary gastrointestinal cause requiring at least 1 month of PN. Before patients began FOLE treatment, other causes of liver disease including hepatitis C, cystic fibrosis, biliary atresia, and α-1 antitrypsin deficiency were excluded and standard therapies were attempted, including serial transverse enteroplasty (STEP) procedure, PN cycling, PN restriction of copper and manganese content, and ursodiol treatment. Cystic fibrosis and biliary atresia were ruled out using immunoreactive trypsinogen assay and ultrasound, respectively. Subjects for this report were consecutive patients who received FOLE for IFALD. The Western IRB in Olympia, WA and the University of Hawaii Human Studies Program approved this retrospective review.

Baseline Characteristics and Clinical Course Prior to FOLE Treatment

Demographic, anthropometric, biochemical, clinical, and dietary information was collected retrospectively from the inpatient electronic medical record. Subject characteristics and clinical course prior to receiving treatment included the primary diagnoses resulting in PN dependence, bowel availability for enteral feeding, age at diagnosis of IFALD, and standard IFALD therapies implemented. Cyclic PN was defined as a daily break from PN of greater than 4 hours.

Patient Outcomes and Clinical Course After FOLE Treatment

Anthropometric, biochemical, clinical, and dietary outcomes were monitored from FOLE treatment through discharge from the hospital. The hospital laboratory conducted all biochemical tests, except for serum fatty acid analyses, which were done by the Mayo Clinic Department of Laboratory Medicine and Pathology (Rochester, Minnesota). Direct bilirubin concentration was determined using a timed endpoint diazo method (Synchron Systems, Beckman Coulter, Brea, California). Enteral and parenteral intakes were analyzed per kilogram of body weight for each subject on a median of 3 days at each time point to accommodate for fluctuations due to the clinical course. Body weight, length, and head circumference were converted into *z* scores for age and sex using the lambda, mu, and sigma technique based on the 2000 Centers for Disease Control and Prevention growth charts.[23] Most of the subjects were born prematurely, so the expected date of delivery was used to establish their adjusted age for this calculation. An episode of line sepsis was defined as the occurrence of 2 positive blood cultures with the provision of antibiotics for 5 days or more.

Statistical Analysis

The proportion of subjects with abnormal values at baseline and 12 weeks was determined based on hospital laboratory reference ranges for biochemical data and the 3rd and 97th percentiles for age and sex for anthropometric parameters. Baseline and follow-up values for biochemical, nutritional, and anthropometric data were compared using the Wilcoxon rank sum test. The relationship between direct bilirubin concentration normalization and length of stay, and the effect of timely initiation of FOLE treatment on these outcomes, were assessed using Spearman's rank correlation coefficient. For these analyses, the diagnosis of IFALD was used as the starting point. All statistical tests were conducted using Statistical Analysis Software (SAS), version 9.2 (Cary, North Carolina), and graphs were prepared using Microsoft Excel for Macintosh 2011, version 14.2.5 (Redmond, Washington). Statistically significant differences were based on a *P* value of less than .05. This study is registered with the US National Institutes of Health clinical trials registry (NCT01194063).[24]

Results

Subject Characteristics and Clinical Course

All subjects required PN from the time of birth, and 90% developed IFALD before 9 weeks of age (Table 1). As seen in Table 1, the underlying causes of intestinal failure and remaining bowel

Table 1.

Demographic Characteristics and Clinical Course of Subjects.

				Age, wk				Sepsis Episodes	
ID	Sex (Race)	Gestational Age, wk	Diagnoses (Intact Bowel)	Dx	Tx	N Bili	D/C	Before Tx	Tx to D/C
1	M (PI)	30.7	Gs/At (Jej: Colon)	2.6	32.6	55.3	65.6	1	4
2	F (As/Hi/PI)	34.9	Gs/At (Jej: Colon)	2.0	36.3	55.6	67.9	5	1
3	F (As)	38.6	Vo/Om/At/NEC (Jej: Colon)	15.3	21.7	28.3	47.4	0	1
4	M (Hi/PI/Wt)	30.0	NEC (Ileostomy)	7.1	16.4	—	—	0	0
5	M (As/PI/Wt)	35.1	At (Jej: Colon)	2.9	15.1	27.1	49.0	0	2
6	M (As/Hi/PI)	38.0	Gs/At (Jejunostomy)	4.9	9.9	29.4	52.1	0	3
7	F (As/Hi/Wt)	36.3	Gs/At (Jejunostomy)	7.9	10.9	15.0	24.6	0	1
8	F (As)	29.0	Perf/At (Jejunostomy)	5.0	10.9	18.4	18.7	0	0
9	M (As/PI/Wt)	31.0	Perf (Duod: Colon)	3.9	9.4	25.3	40.4	0	1
10	F (As/Wt)	27.6	Vo/NEC (Jejunostomy)	8.1	16.7	27.9	28.4	0	0

Abbreviations: As, Asian; At, intestinal atresia; D/C, discharge from hospital; Duod, duodenum; Dx, diagnosis with IFALD; Gest, gestation; Gs, gastroschisis; Hi, Hispanic; IFALD, intestinal failure–associated liver disease; Jej, jejunum; N Bili, normalization of direct bilirubin; NEC, necrotizing enterocolitis; Om, omphalocele; Perf, intestinal perforation; PI, Pacific Islander; Tx, treatment with fish oil–based lipid emulsion; Vo, volvulus; Wt, white.

anatomy varied substantially. Subjects had IFALD for a median of 6.1 (3.0-12.3) weeks before starting treatment with FOLE, except for 2 subjects who had IFALD for 30 or more weeks when the Omegaven protocol was introduced (ID numbers 1 and 2 in Table 1). The requirement for subjects to weigh at least 3 kg in this study was the most common cause of treatment delays among subjects who developed IFALD once the Omegaven protocol was in place. In the interim, several approaches to reduce cholestasis and prevent further liver injury were used, including cycling of PN (90%), restriction of copper and manganese (90%), ursodiol administration (30%), and STEP surgery (20%).

During the treatment follow-up period, the 4 subjects with diverting jejunostomies had surgery to restore bowel continuity at weeks 2, 3, 8, and 20. One subject underwent repeat STEP surgery at week 10 that was estimated to increase the small bowel length from 50 to 68 cm (ID number 1 in Table 1).

Another subject was transferred temporarily to another institution for intestinal transplantation evaluation and received Intralipid for nearly 6 weeks (ID number 9 in Table 1). As seen in Table 1, the number of episodes of sepsis before and after starting FOLE treatment was generally quite minimal.

Of the 10 subjects in this study, 1 died at 31 weeks of life due to chronic lung disease complications (ID number 4 in Table 1). The surviving 9 subjects were discharged from the hospital 7.9 to 42.3 weeks after starting treatment. Discharge was determined by clinical stability and arrangements for transfer home. At the time of discharge, most of the subjects (78%) were still PN-dependent and continued to receive FOLE as outpatients.

Biomarkers of Liver Disease

Table 2 summarizes changes that occurred during the first 12 weeks of treatment. The laboratory values at baseline were consistent with the diagnosis of liver disease with elevated concentration of liver enzymes in many of the patients. By week 6 of treatment, direct bilirubin concentrations were reduced significantly ($P = .037$), and values continued to decrease to a low of 3.1 (0.1-6.3) mg/dL by week 12 with one-third of subjects having normal direct bilirubin values (Figure 1). None of the other liver disease biomarkers parameters changed significantly after 12 weeks of treatment, including prothrombin time and international normalized ratio, which were measured at various times during the FOLE course ($P < .05$, data not shown).

Direct bilirubin concentrations normalized 12.0 (4.1-22.7) weeks after starting treatment (Table 1). A quicker resolution of cholestasis was associated with a decreased length of stay (Spearman's $\rho = 0.810$, $P = .015$). Although direct bilirubin concentrations decreased after starting treatment (Figure 1), earlier initiation of FOLE following IFALD diagnosis was not associated with more rapid normalization of direct bilirubin

Table 2.

Anthropometric and Biochemical Characteristics at Baseline and After 12 Weeks of Fish Oil–Based Lipid Emulsion Treatment.[a]

		Baseline			Week 12			
Variable	Normal	n	Value	Abnormal	n	Value	Abnormal	*P* Value
Weight, *z* score	−1.88 to 1.88	10	−1.64 (−4.48 to 0.21)	4/10 (40%)	10	−1.11 (−2.42 to 0.22)	2/10 (20%)	.174
Length, *z* score	−1.88 to 1.88	10	−1.82 (−4.41 to 0.18)	5/10 (50%)	8	−1.55 (−4.96 to 0.15)	3/8 (38%)	.790
HC, *z* score	−1.88 to 1.88	9	−1.91 (−4.13 to −0.72)	5/9 (56%)	7	−1.69 (−3.30 to 0.65)	2/7 (29%)	.491
Albumin, g/dL	4.0 to 5.1	10	3.5 (2.8 to 4.7)	8/10 (80%)	9	3.6 (2.8 to 4.4)	7/9 (78%)	.566
ALT, U/L	7 to 51	10	145 (38 to 362)	9/10 (90%)	9	145 (18 to 561)	7/9 (78%)	.870
GGTP, U/L	12 to 72	10	131 (32 to 281)	7/10 (70%)	8	219 (49 to 366)	7/8 (88%)	.110
ALP, U/L	82 to 383	10	337 (216 to 661)	4/10 (40%)	9	316 (188 to 562)	3/9 (33%)	.870
Triglycerides, mg/dL	<150	10	187 (76 to 501)	7/10 (70%)	9	129 (54 to 241)	3/9 (33%)	.060
Platelet count, $\times 10^9$	≤100	9	173 (81 to 498)	2/9 (22%)	7	193 (112 to 339)	0/7 (0%)	.560
CRP, mg/L	<1.0	9	8.0 (3.9 to 36.4)	9/9 (100%)	5	3.4 (0.4 to 49.1)	4/5 (80%)	.386

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; CRP, C-reactive protein; GGTP, γ-glutamyl transpeptidase; HC, head circumference.
[a]Weight, length, and head circumference *z* scores for age and sex determined using lambda, mu, and sigma method based on 2000 Centers for Disease Control and Prevention growth charts and prematurity-adjusted age.[23] The normal range of *z* scores corresponds to the 3rd and 97th percentiles for age and sex. The normal ranges for laboratory values were based on reference values provided by the hospital laboratory. Values are presented as median (range) for continuous variables.

(Spearman's ρ = 0.571, $P = .139$). However, a longer delay in FOLE treatment did trend toward a significant correlation with an increased length of hospital stay (Spearman's ρ = 0.690, $P = .058$). The subject who died and the subject who received soybean oil–based lipid emulsion for 6 weeks during the treatment period were not included, leaving only 8 subjects for these analyses.

Fatty Acid Profile

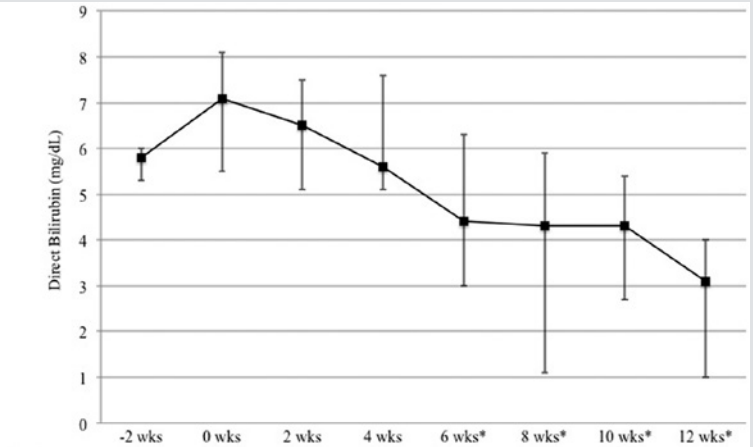
The summary of fatty acid profile changes is shown in Table 3. FOLE treatment was associated with a significant increase in ω-3 fatty acids and decrease in ω-6 fatty acids ($P < .05$) within 4.0 to 13.0 weeks of starting treatment. However, there was no evidence of essential fatty acid deficiency (triene/tetraene ratio >0.2), and the mead acid concentrations and triene/tetraene ratios were relatively stable during this time. One subject (ID number 4 in Table 1) had a notably higher mead acid concentration of 99.0 µmol/L and triene/tetraene ratio of 0.124 at baseline, which decreased to 24.0 µmol/L for mead acid and 0.046 for triene/tetraene ratio after 30 days of FOLE treatment. Importantly, enteral feedings were initiated in this subject between week 2 and week 4 after starting FOLE treatment, which may have contributed to the apparent resolution of essential fatty acid deficiency.

Nutrition and Growth

As seen in Figure 2, the 12-week period following initiation of treatment was marked by a dramatic shift in enteral and parenteral intake. Enteral intake increased significantly, whereas parenteral intake tended to decrease, albeit to a lesser extent, resulting in a net increase in energy intake. At the end of the 12 weeks, most subjects (80%) had reduced requirements for PN as a result of increasing enteral tolerance. Moreover, 2 of the surviving subjects (22%) were no longer PN dependent at discharge (ID numbers 7 and 8 in

Figure 1.

Biweekly Direct Bilirubin Concentrations in Subjects in Relation to Fish Oil–Based Lipid Emulsion Treatment.



	-2 wks	0 wks	2 wks	4 wks	6 wks*	8 wks*	10 wks*	12 wks*
Median	5.8	7.1	6.5	5.6	4.4	4.3	4.3	3.1
n	9	10	10	10	9	9	9	9
n <2.0 mg/dL	0	0	0	1	2	3	2	4

Data points indicate medians; error bars indicate interquartile ranges. Changes in direct bilirubin concentrations were assessed using Kruskal-Wallis test ($P = .001$), and each time point was compared to baseline using the Wilcoxon rank sum test (*$P < .05$).

Table 3.

Comparison of Serum Lipid Profiles Before and After Treatment With Fish Oil–Based Lipid Emulsion.

Variable	Before	After	Reference	*P* Value
n	8	9		
Timing[a], d	–3 (–19 to 1)	31 (30-91)		
ω-3, mmol/L	0.7 (0.2-1.0)	3.3 (1.2-7.5)		<.001
ω-6, mmol/L	5.4 (2.2-6.7)	3.1 (1.7-4.6)		.004
ω-6:ω-3 ratio	8.7 (6.6-13.5)	0.8 (0.5-3.0)		<.001
ALA, μmol/L	4429 (1111-5600)	2383 (1282-3662)	10-190	.016
LA, μmol/L	219 (38-295)	77 (30-184)	1000-3300	.027
EPA, μmol/L	76 (33-150)	1631 (516-3706)	2-60	<.001
DHA, μmol/L	265 (59-421)	1346 (442-3205)	10-220	<.001
AA, μmol/L	890 (463-1641)	564 (333-1075)	30-120	.034
MA, μmol/L	11.5 (10.0-99.0)	10.0 (4.0-24.0)	3-24	.135
T:T ratio	0.014 (0.011-0.124)	0.016 (0.011-0.046)	≤0.2	.528

Abbreviation: AA, arachidonic acid; ALA, α-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; MA, mead acid; T:T, triene/tetraene.
[a]Timing of blood sample is in relation to the initiation of treatment. Reference values were obtained from the analytic laboratory for fatty acid concentrations, and the published literature for T:T ratio.[17,18] Values are presented as median (range) for continuous variables. Lipid profile before and after treatment were compared using Wilcoxon rank sum test.

Table 1). Although the dose of FOLE was set at 1 g/kg/d, the transition from soybean oil–based lipid emulsion did not result in a significant reduction in intravenous lipids ($P > .05$). This appears to be related to a decrease in PN lipid of 1 g/kg/d or more after diagnosis of IFALD that occurred for all subjects (data not shown). Four of the subjects (ID numbers 6 and 8-10 in Table 1) received some breast milk in their enteral feeds during the treatment period.

The nutrition provided during FOLE treatment was sufficient to support normal growth. At baseline, even after adjustment for prematurity, subjects tended to have lower than normal weight, length, and head circumference for age and sex, with 40% or more falling below the 3rd percentiles for each parameter (Table 2). After 12 weeks of treatment, the median weight, length, and head circumference *z* scores for age and sex increased, and the proportion of subjects below the third percentile of weight, length, and head circumference for age and sex decreased (Table 2). While these improvements in anthropometric measurements suggest catch-up growth, none of these changes were statistically significant ($P > .05$).

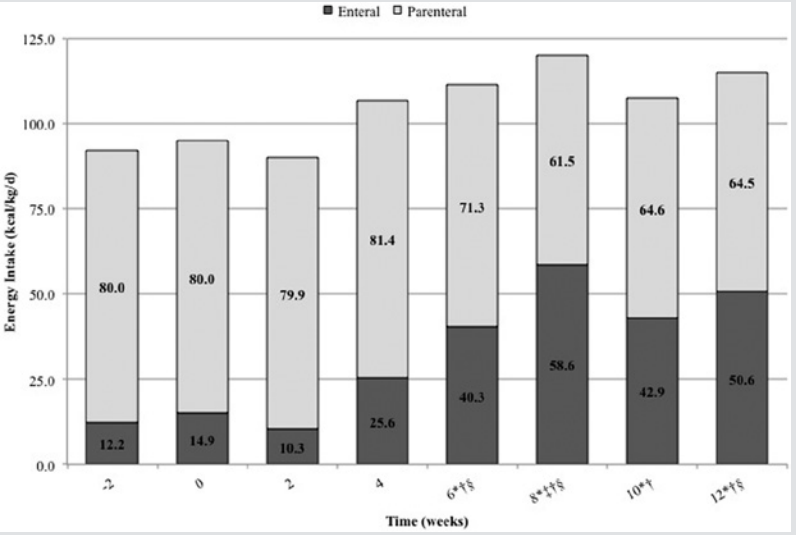
Discussion

The results of this study contribute to the growing literature on the use of FOLE in infants with IFALD. This is one of the larger case series and includes clinically relevant outcomes not provided in previous reports.[16-21] The summary of findings provides important information on the clinical progression of patients with IFALD treated with FOLE.

As expected, within 6 weeks of initiating treatment, direct bilirubin concentrations had significantly decreased, indicating resolution of cholestasis. Factors other than FOLE treatment may have contributed to the normalization of direct bilirubin concentrations in these subjects. Most notably, there was a concomitant transition from parenteral to enteral feeding, which has been found to promote direct bilirubin

Figure 2.

Biweekly Enteral and Parenteral Energy Intake of Subjects in Relation to Fish Oil–Based Lipid Emulsion Treatment.



Values missing for 1 subject at weeks 4, 6, and 8. Each time point was compared to baseline using Wilcoxon rank sum test (*$P < .05$ enteral intake; ‡$P < .05$ parenteral intake; †$P < .05$ enteral to parenteral ratio; §$P < .05$ total intake).

normalization.[16,25] However, it has been proposed that the improvements in enteral tolerance occur secondary to cholestasis resolution resulting from the change to FOLE treatment from vegetable oil–based lipid emulsions.[16,19] Supporting this hypothesis, fish oils contain none of the phytosterols found in conventional vegetable oils that have been shown to inhibit bile acid production resulting in reduced bile flow.[26] In this study, a temporal relationship between direct bilirubin and enteral intake could not be discerned as the changes in both variables began on average at week 4 and became significant at week 6. Although reanastomosis and STEP procedures also have the potential for improving enteral tolerance and bile absorption, only 2 of these procedures preceded the normalization of direct bilirubin, limiting the effect that this might have had on the resolution of cholestasis.[27] Finally, it is possible that improvements in direct bilirubin concentration and enteral feeding reflect normal disease progression or other ongoing IFALD treatments (eg, PN cycling, PN lipid restriction, PN restriction of copper and manganese) and would have occurred without FOLE treatment. While this factor could be tested by comparison to a historical cohort of IFALD patients, this approach was not used here because of the variable delay in initiating FOLE treatment, in addition to changes in disease management over time that would bias such comparisons.

Historically, the fatty acid composition and dose restriction associated with the use of FOLE were thought to present risks for essential fatty acid deficiency and growth impairment.[28-30] Since this time, numerous case series and case-control studies have been published demonstrating that essential fatty acid levels[17-21] and anthropometric measurements of growth[17,19] remain normal in patients receiving FOLE. The results of this study support these earlier findings in a multiethnic cohort of formerly preterm infants with short bowel syndrome. Importantly, all but 1 subject received some enteral nutrition support that provided ω-6 fatty acid intake. To date there are no reports of clinically significant fatty acid deficiencies associated with the use of FOLE in infants, even among patients who received no enteral feeding.[18] However, the long-term effects of a 1.0-g/kg dose of FOLE in infants on growth and cognitive development requires further investigation.

Length of hospital stay is an important clinical outcome that had not been considered in prior case series or case-control studies.[16-21] The average cost of hospitalization for neonates with short bowel syndrome was estimated to be approximately $416,818 for 119 days, providing considerable monetary incentive for interventions that reduce length of stay.[31] In this study, subjects who had a more rapid return of direct bilirubin concentrations to normal levels were discharged from the hospital earlier. Unlike previous reports,[15] earlier initiation of FOLE treatment after the diagnosis of IFALD did not appear to reduce the duration of cholestasis but may have contributed to a decrease in length of stay. The requirement for subjects to weigh at least 3 kg was the most common delay in starting FOLE and was set by the FDA based on the quantity of blood obtained from patients for monitoring of biochemical indices as per the Omegaven treatment protocol at the Kapi'olani Medical Center for Women and Children. This restriction does not appear to be a factor in other institutions,[32] which may lower the external validity of our findings.

The information in this case series add to the growing body of evidence supporting the safety and positive outcomes in infants with short bowel syndrome and IFALD treated with FOLE. A reduction in length of hospital stay may be an important clinical benefit of early FOLE intervention, although this association may have been confounded by external factors that caused the delay in FOLE treatment. Some of these patients were able to transition off PN to full enteral feeds, and all surviving patients have been discharged from the hospital with normal growth and without developing

essential fatty acid deficiency. A concomitant reduction in direct bilirubin levels and enteral nutrition tolerance occurred after 4 weeks of treatment, but the exact relationship between these outcomes in relation to the use of FOLE is still unclear. Many questions remain, particularly in smaller and younger infants who are at risk for IFALD due to intestinal complications and immature bowel function. Additional studies on safety, dosage, timing, and potential combination therapy are needed to achieve optimal intestinal and growth outcomes especially in the high risk infant populations.

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Author Note

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