Published in final edited form as:

J Pediatr Gastroenterol Nutr. 2015 March ; 60(3): 375–377. doi:10.1097/MPG.0000000000000609.

Preservation of Biochemical Liver Function With Low-Dose Soy-Based Lipids in Children with Intestinal Failure Associated Liver Disease

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Abstract

Objectives—Intestinal failure associated liver disease (IFALD) contributes to significant morbidity in pediatric intestinal failure (IF) patients. However, the use of parenteral nutrition (PN)

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Conflicts of interest and source of funding:

None of the authors have any relevant financial disclosures and no external funding was utilized for this project

with a fish oil-based IV emulsion (FO) has been associated with biochemical reversal of cholestasis and improved outcomes. Unfortunately, FO increases the complexity of care: as it can only be administered under FDA compassionate use protocols requiring special monitoring, is not available as a 3-in-1 solution and is more expensive than comparable soy-based lipid formulation (SO). Due to these pragmatic constraints a series of patient families were switched to low-dose (1g/kg/day) SO following biochemical resolution of cholestasis. This study examines if reversal of cholestasis and somatic growth are maintained following this transition.

Methods—Chart review of all children with IFALD who switched from FO to SO following resolution of cholestasis. Variables are presented as medians (interquartile ranges). Comparisons performed using Wilcoxon signed-rank test.

Results—7 patients aged 25.9 (16.2,43.2) months were transitioned to SO following reversal of cholestasis using FO. At a median follow up 13.9 (4.3,50.1) months there were no significant differences between pre- and post-transition serum alanine and aspartate aminotransferases, direct bilirubin, and weight-for-age z-scores. Due to recurrence of cholestasis, one patient was restarted on FO after four months on SO.

Conclusions—Biochemical reversal of IFALD and growth were preserved after transition from FO to SO in 6/7 (86%) patients. Given the challenges associated with the use of FO, SO may be a viable alternative in select home PN patients.

Keywords

Short bowel syndrome; Intestinal failure associated liver disease; Parenteral nutrition associated liver disease; Soy based lipid emulsions; Intravenous Fish oil

Introduction

Intestinal failure (IF) is a condition characterized by insufficient bowel function to maintain hydration and nutrient absorption for growth and development (1). In these patients, parenteral nutrition (PN) is a life sustaining therapy that has dramatically improved outcomes (2). However the development of cholestasis has long been recognized as a significant cause of morbidity and mortality for those on long-term PN (3,4). The risk of intestinal failure associated liver disease (IFALD) advancing to end stage liver disease (ESLD) has been reported as high as 25% (5) and is a major cause of mortality in children with IF (5,6,7).

Though outcomes have improved substantially with the advent of multidisciplinary intestinal rehabilitation programs and other therapeutic advances, (8,9) IFALD still represents a major challenge. Some investigators have demonstrated a reduction in the incidence and progression of liver disease by limiting soy-based IV lipid emulsions (SO) to 1gm/kg/day or less however in the absence of large multi-center randomized controlled trials lipid restriction strategies are not uniformly applied (10,11). The use of fish oil-based lipid emulsion (FO), such as Omegaven® (Fresenius Kabi, Bad Homburg, Germany) in place of SO have also been associated with resolution of direct hyperbilirubinemia (12,13). This reversal of cholestasis is thought to be due to the differences in the composition of fish oil- and soy-based IV lipid formulations. Unlike SO, FO contain the omega-3 fatty acids:

docosahexaenoic acid (DHA) and eicosapentanoic acid (EPA) which may have anti-inflammatory properties (11,14). Commercially available FO formulations contain supplemental vitamin E, which may also decrease inflammation. On an additional note FO formulas do not have phytosterols (such as stigmasterol, β -sitosterol, and campesterol) which are present in SO. Of significance phytosterols suppress expression of canalicular bile transporters thereby potentially promoting cholestasis and liver disease (15,16).

Intravenous FO has not yet been approved by the Food and Drug Administration (FDA) and therefore is available only as a rescue therapy under compassionate-use protocols. Hence it may be prescribed only in the setting of rigorous monitoring. Additionally in the absence of compatibility data, FO cannot be combined into the same bag as PN (i.e. a 3-in-1 solution) and the simultaneous delivery of other intravenous medications is also restricted. At present the use of FO therefore requires an increased frequency of access of the central venous catheter. While available evidence does not implicate the use of FO with an incremental risk of catheter related blood stream infection (CRBSI) additional manipulations of central venous lines needed for FO delivery may potentially increase infection risk (17). Finally while some institutions have been able to obtain insurance coverage for FO therapy, for many this remains a continuing challenge. Even if all of these logistic issues were solved FO remains a more expensive therapy than SO due to the increased manufacturing complexity.

Consequently some patient families at our center switched to low dose SO (1g/kg/day) after biochemical resolution of IFALD was achieved on FO. In the literature there is a paucity of long term data for patients switched from FO to SO (18, 20). The current study is unique as it aims to evaluate if the transition to SO after FO therapy preserves the resolution of cholestasis and maintains somatic growth in children with IFALD.

Materials and Methods

Following Institutional Review Board approval (M06-01-0049), records of 378 children with IF managed by the Center for Advanced Intestinal Rehabilitation (CAIR), the multidisciplinary intestinal rehabilitation program at Boston Children's Hospital, were reviewed. The protocol for compassionate use of FO defined IFALD as direct bilirubin > 2 mg/dL for 2 consecutive weeks in the setting of PN exposure and absence of other underlying diagnoses explaining liver abnormalities. Pediatric IF patients with established IFALD whose bilirubins normalized after treatment with FO and were then switched to low dose SO were included. Clinical and laboratory characteristics at three specific time points were recorded: initiation of FO, immediately prior to switching to low dose SO, and at the most recent follow-up visit. Weight for age z-score (WAZ) was calculated using World Health Organization (WHO) charts for children $\leq$ 2 years of age whereas Centers for Disease Control (CDC) charts were used for those greater than 2 years of age. Residual small bowel length was measured along the anti-mesenteric border. Categorical data are summarized with frequency counts and percentages and continuous data are presented as medians with interquartile ranges. Statistical analysis was performed using JMP (SAS Institute, Cary, NC). Continuous variables were compared by Wilcoxon signed-rank tests.

Results

Seven patients with IFALD were transitioned to low dose SO after a median of 20.7 (8.5–26.6) months of FO therapy. Prior to the transition, all patients had evidence of biochemical resolution of cholestasis (total bilirubin <2.0 mg/dl) for 20.7 (7.5–24.2) months. Following transition, median duration of follow up was 13.9 (4.3, 50.1) months. All patients were premature [median estimated gestational age (EGA) 33 (26–36) weeks]. Gastroschisis was the most frequent underlying diagnosis leading to IF. All but one of the patients underwent at least one bowel resection. The remaining patient had deferred repair of duodenal atresia (duodenoduodenostomy) at 4 months of life as a result of prematurity (EGA 25 weeks) and severe respiratory distress syndrome. Median residual bowel length was 32 (19.5–40) cm and median serum citrulline level was 9.5 (7.3–11) μ mol/L. At initiation of FO all patients had evidence of IFALD as evidenced by a median direct bilirubin (DB) of 3.5 (3.1–7.0) mg/dL and aspartate aminotransferase to platelet ratio (APRI) of 1.06 (0.54–2.34) (19). Demographic, clinical, and laboratory characteristics of the patients studied are presented in Table 1. Tolerance of enteral nutrition (EN) as determined by the percentage of total calories administered enterally was similar at all three time points; prior to initiating FO, preceding transition to SO and at the most recent follow-up ($p=0.31$). Clinical and laboratory parameters preceding transition to SO compared to those obtained at the most recent follow-up did not reveal any statistically significant differences in alanine aminotransferase ($P=0.68$), aspartate aminotransferase ($P=1.0$), DB ($P=1.0$), total bilirubin ($P=0.25$), and WAZ ($P=0.31$) (Figure 1). 1 of the 7 (14%) patients was reinitiated on FO in the setting of worsening liver function tests (LFTs) 4 months after the transition to SO (peak total bilirubin 6.6mg/dL, direct bilirubin 5.0 mg/dL, aspartate aminotransferase 130 mg/dL and alanine aminotransferase 68mg/dL). None of the children studied developed biochemical evidence of essential fatty acid deficiency (normal triene-tetraene ratios, Table 2).

Discussion

Following transition to low dose SO, the majority of children reviewed (6/7) demonstrated long-term preservation of LFTs. The one patient with elevation of bilirubin was reinitiated on FO following which biochemical resolution of cholestasis occurred. Overall for the whole group there were no statistically significant changes in the LFTs. Although there was an increase in alanine aminotransferase levels post transition this did not achieve statistical significance due to the overlap in the interquartile ranges. Alanine aminotransferase appears to be a particularly sensitive indicator of hepatocyte injury in children with IFALD (20). Enteral feeding is known to stabilize and reverse the biochemical changes associated with IFALD, however, during the course of this study there was no significant change in the percentage of enteral nutrition administered (21).

Weight for age z score (WAZ), a marker of nutritional status, remained unaffected by the switch from FO to SO implying preserved somatic growth. Analogous to other studies restriction of parenteral lipid emulsions to 1g/kg/day as FO or SO was not associated with biochemical essential fatty acid deficiency (22).

The single patient with rebound elevation in serum bilirubin following transition to low dose SO was carefully reviewed in an effort to identify any factors responsible. The primary diagnosis leading to IF in this patient was congenital multiple intestinal atresias (MIA) syndrome with severe combined immunodeficiency (SCID), associated with a TTC7A mutation. MIA is associated with an extremely poor outcome and the disorder is usually fatal within the first month of life (23). This patient had a long term survival due to early identification and allogenic bone marrow transplantation as well as repair of all his small bowel atresias and creation of an end stoma. Prior to initiation of FO he underwent a liver biopsy that demonstrated marked fibrosis with portal to portal bridging. FO therapy was used for a total of 28 months, which led to a reduction of serum bilirubin levels to less than 2mg/dL. Following the transition to SO he was noted to have worsening LFTs including elevated serum bilirubin levels as a consequence he was reinitiated on FO therapy. Of note this increase in bilirubin was seen in the absence of any significant metabolic derangements or septic events. He underwent a repeat biopsy just before the re-initiation of FO therapy that re-demonstrated marked fibrosis with findings congruent with IFALD. After resumption of FO patient's direct hyper-bilirubinemia gradually resolved over the course of eight months. He remains on FO therapy.

Limitations of this case series include its retrospective design, small number of patients and variable follow up period. Despite these limitations the median duration of follow up (14 months) in this series significantly exceeds the 1–4 week period during which the biochemical changes associated with IFALD typically become apparent (24,25). In this study biochemical resolution of cholestasis and growth were generally preserved after the transition from FO to SO. Given the practical issues associated with the administration of FO, more extensive prospective analysis of this therapeutic approach appear warranted.

Acknowledgments

Sources of support:

CD received funding from NICHD 5K24HD058795. No other relevant acknowledgements.

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Figure 1.
Clinical and Laboratory Parameters Pre- and post transition from FO

Table 1

Patient Characteristics

Characteristic	Median	IQR
Gestational Age (weeks)	33	26–36
Age * (months)	5.2	2.5–7.7
Bowel Length (cm)	32	19.5–40
Citrulline * (μmol/L)	9.5	7.3–11
ALT* (mg/dL)	124	55–288
AST* (mg/dL)	161	63–327
D.Bilirubin * (mg/dl)	3.5	3.1–7
T.Bilirubin * (mg/dL)	4.9	4.05–9.9
APRI*	1.06	0.54–2.34
Duration of FO therapy (months)	20.7	8.5–26.6
Duration of Follow up (months)	13.9	4.3–50.1

* Values obtained at initiation of Fish oil therapy

ALT= Alanine aminotransferase

AST= Aspartate aminotransferase

APRI= aspartate aminotransferase to platelet ratio index.

Table 2

Patient characteristics pre- and post transition to low dose soy-based IV lipid emulsion.

Variable	FO* Median (IQR)	SO** Median (IQR)	p-value
ALT (mg/dL)	36 (23.5–63)	71 (25–75)	0.68
AST (mg/dL)	46 (33–66.5)	57 (36–84)	1.00
D.Bilirubin (mg/dL)	0.2 (0.1–0.3)	0.1 (0.1–0.3)	1.00
T.Bilirubin (mg/dL)	0.4 (0.3–0.9)	0.4 (0.3–1.0)	0.25
WAZ***	–2.10	–1.54	0.24
Triene-tetraene ratio	0.017 (0.0135–0.018)	0.026 (0.02–0.039)	0.13

* Values represent medians for each variable obtained immediately prior to switching from FO to SO.

** Values represent medians for each variable obtained at the last follow up following transition to SO.

*** Values represent means