

Novel Lipid-Based Approaches to Pediatric Intestinal Failure–Associated Liver Disease

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Historically, intestinal failure–associated liver disease (IFALD) has been the greatest contributor to the morbidity experienced by children with intestinal failure. Although the cause of IFALD is multifactorial, recently much attention has been devoted to the critical role that intravenous lipid emulsions play in the development of IFALD. This attention has prompted an interest in alternate approaches to the provision of intravenous lipid in children with IFALD. The 2 approaches that have been advanced are that of lipid minimization and alternate intravenous lipid emulsions, including those containing ω -3 fatty acids. This article examines the rationale and current evidence for these approaches in children with intestinal failure. Our overall finding is that although these alternate approaches show significant promise, they have primarily been studied in uncontrolled settings, mainly in children with advanced IFALD. As such, we believe that there remains a lack of definitive evidence for their efficacy. Furthermore, important safety parameters remain to be evaluated, including the effect of these therapies on growth and development. Therefore, there is currently insufficient evidence to support the use of these novel therapies as standard of care in children with no or early IFALD with the goal of preventing the progression of liver disease.

Arch Pediatr Adolesc Med. 2012;166(5):473-478

Intestinal failure–associated liver disease (IFALD) is one of the greatest contributors to the morbidity experienced by children with intestinal failure (IF).^{1,2} Although the cause of IFALD is multifactorial, including host factors such as prematurity and sepsis and components of parenteral nutrition (PN), recently the key role that intravenous lipid emulsions (ILEs) play has been recognized.³⁻⁵ Conventional ILEs (derived from plant-based lipids, primarily soy) are thought to contribute to the development of IFALD through a number of mechanisms, including accumulation of phospholipids,⁶ excess phytosterols,⁷⁻⁹ predominance of ω -6 fatty acids (ω -6FAs) that

are proinflammatory,¹⁰⁻¹² and antioxidant imbalance related to inadequate provision of alpha tocopherol.^{13,14} Given this, there is substantial interest in alternate approaches to the provision of intravenous lipid in children with IF. The 2 primary approaches that have been advanced are lipid minimization and the use of ILEs containing ω -3 fatty acids (ω -3FAs), which are derived from fish oil. Furthermore, ILEs derived from other sources could be used to replace the soy-based emulsions. This review considers the rationale and current evidence for these novel lipid-based treatment approaches in children with IFALD.

LIPID MINIMIZATION

Definition and Rationale

Current recommendations for PN lipids, for infants who are dependent on PN, is 2 to 3 g/kg daily.^{15,16} These recommenda-

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tions are revised from the historical upper limit of 4 g/kg daily. Lipid minimization refers to provision of a soy-based ILE in doses significantly lower than these recommendations. Although no consistent definition of lipid minimization exists, we have defined this to be an intravenous lipid dose, in a child receiving full (>60% of total calories) parenteral support, of less than 1 g/kg daily. However, lipid minimization has been used with intravenous lipid intakes lower than this range. Therefore, we regard our definition to be the upper range for what constitutes lipid minimization. The rationale for lipid minimization relates to the notion that lowering parenteral lipid exposure lessens the risk of IFALD.¹⁷

Clinical Experience With Lipid Minimization

Evidence of the utility of lipid minimization is limited and comes only from retrospective or uncontrolled studies. Despite this, the weight of evidence suggests that cholestasis may be improved by a reduction in lipid dose. Colomb et al¹⁸ demonstrated an association between decreases in lipid therapy and normalization of serum conjugated bilirubin (CB). Rollins et al¹⁹ described 6 children with IFALD in whom the soy-based ILE was stopped, with subsequent resolution of cholestasis in all. However, 4 of the 6 patients received an enteral fish oil preparation, which raises the possibility of an ω -3FA effect or that resolution of cholestasis may be partly related to improved enteral tolerance.²⁰ Torres et al²¹ described 32 patients with IFALD, of whom 31 normalized their hyperbilirubinemia with aggressive intestinal rehabilitation that included restriction of a soy-based ILE to less than 1 g/kg daily. Bianchi²² suggested improved outcomes with a "hepato-sparing regimen" with an ILE dose less than 1.5 g/kg daily. The group from the University of Michigan described a consecutive series of 32 surgical patients receiving PN, with a CB level greater than 2.5 mg/dL or a total bilirubin level greater than 5 mg/dL (to convert bilirubin to micromoles per liter, multiply by 17.104), who were enrolled in a lipid minimization protocol.¹⁷ Children in this series received 1 g/kg of a plant-based ILE twice a week. Fourteen patients were compared with 14 matched historical controls, with the restricted group demonstrating a mean reduction in serum CB of 0.9 mg/dL per week of therapy.

ω -3 LIPIDS

Rationale

In contrast to ω -6FAs, ω -3FAs have a number of beneficial effects that are proposed to ameliorate IFALD.⁵ Fish oil-derived ILEs have been demonstrated in an animal model not to impair bile flow.⁷ This finding may be related to either a reduction in phytosterols or via prostaglandin-mediated mechanisms related to the addition of ω -3FAs.^{7,23,24} In addition, ω -3FAs reverse hepatic steatosis in both PN and non-PN liver disease^{25,26} and decrease oxidative stress.²⁷ The effect on oxidative stress is augmented by the fact that many of the ILEs containing ω -3FAs also have significantly more of the antioxidant alpha-tocopherol than conventional emulsions.^{13,14,28} Finally,

ω -3FAs have important immunomodulatory effects, resulting in fewer proinflammatory mediators.^{10-12,29}

Clinical Experience With ω -3-Containing ILEs

Experience With Omegaven. Gura et al,³⁰ from Children's Hospital Boston, published the first report of 2 children with severe end-stage IFALD who demonstrated complete IFALD reversal after a change from soy-based Intralipid (Fresenius Kabi) to Omegaven (Fresenius Kabi), a fish oil-derived ILE. The most recent detailed publication of outcomes from this group focuses on 42 infants who received Omegaven compared with 49 individuals from a historical cohort.³¹ Overall resolution of cholestasis while receiving PN in the Omegaven group was 19 compared with 2 in the control group. The risk of death or transplantation was also substantially lower in the Omegaven group (4 of 42 vs 17 of 49). However, follow-up was short, and 25% of children in the cohort received PN for fewer than 3 weeks, which limits the interpretability of these results. A recent review³² states that more than 130 children have received Omegaven at Children's Hospital Boston with good results.

To date, 33 patients have received Omegaven at our institution, with the outcome of the first 22 analyzed in detail.^{33,34} The median age at initiation of Omegaven use was 6.9 (range, 2.2-46) months. Median CB level at the start of therapy was 6.7 mg/dL (range, 3.2-13.5 mg/dL). Sixteen patients (73%) had complete and sustained resolution of hyperbilirubinemia. Four patients received a transplant before resolution of hyperbilirubinemia and 2 died (1 of IFALD and 1 of neurologic insult). In contrast to our historical liver failure mortality rate of 22% per year of infants with IF,³⁵ only 1 infant has died of IFALD since starting to use Omegaven in 2006.

Whereas the group in Boston only provides 1 g/kg of Omegaven as the sole parenteral lipid source, we have pursued combination therapy by mixing Omegaven (1 g/kg) with Intralipid (1 g/kg). We believe that the mixture provides for improved growth and more closely approximates normal fatty acid intake and is therefore more physiologic.

Other reports on the use of Omegaven to treat pediatric IFALD are limited to case series and single patient reports with outcomes similar to that noted in our and the Boston experience.³⁶⁻⁴² There has also been discussion of the possible beneficial effects of enteral fish oils.⁴³ Although enteral preparation use is partly related to the difficulty of obtaining Omegaven in North America, these reports are substantially confounded by the fact that children with sufficient intestinal function to tolerate enteral fish oil are likely demonstrating adequate intestinal adaptation. Therefore, IFALD resolution may be due to improved enteral tolerance.²⁰

Experience With SMOFlipid. SMOFlipid (Fresenius Kabi) is a composite ILE that contains soy bean oil (30%), medium chain triglycerides (MCT) (30%), olive oil (25%), and fish oil (15%). The product has an n6:n3 ratio (ratio of ω -6FAs to ω -3FAs) of 2.5:1. The lipid composition of SMOFlipid more closely approximates the composition of breast milk than does Intralipid (**Figure**).

A number of studies have examined SMOFlipid relative to standard soy-based lipids in pediatric populations, including preterm infants, at doses of lipid up to 3.5 g/kg daily.⁴⁴⁻⁴⁷ The results of these studies have confirmed the safety of SMOFlipid and it being a suitable replacement for a soy-based lipid. Some of the outcomes from these trials are of direct relevance to children with IFALD. Skouroliaou et al⁴⁷ demonstrated reduced oxidative stress with SMOFlipid relative to Intralipid in a randomized controlled trial of 38 preterm infants. However, serum bilirubin levels did not differ at day 14 of treatment. Tomsits et al⁴⁵ compared SMOFlipid to Intralipid in 60 premature neonates and demonstrated improvements in serum γ -glutamyl transferase with SMOFlipid. Goulet et al⁴⁴ studied 28 children receiving home PN randomized to receive SMOFlipid vs Intralipid for a month. At the end of this period, whereas the total bilirubin levels had decreased in the SMOFlipid group during the trial, total bilirubin levels had increased in the Intralipid group. Finally, there are 3 case series from Europe of SMOFlipid being used for the management of advanced IFALD, much in the same way that Omegaven has been used in North America.⁴⁸⁻⁵⁰ Of the 23 patients treated across these 3 series, 18 demonstrated complete resolution of their conjugated hyperbilirubinemia despite receiving conventional doses of lipid.

OTHER ALTERNATE ILES

Outside North America, there are other emulsions, including mixtures of soy and coconut (Lipofundin MCT; B. Braun) and olive and soy (Clinoleic; Baxter).⁵¹ By reducing ω -6FA exposure, these emulsions may play a role in the management of IFALD.

There is one randomized study of Lipofundin MCT in pediatric surgical patients that is not of particular relevance to those with IF.⁵² There was also a 3-day trial of Lipofundin MCT vs a soy-based emulsion that did not demonstrate differences in total bilirubin; however, the duration of the study was too short for a difference to be expected. On the basis of fatty acid profiles, the authors concluded that the conventional emulsion may be preferred from a nutritional perspective.⁵³ A recent 7-day randomized study of Lipofundin MCT vs Lipoplus (B. Braun), an emulsion with similar composition to SMOFlipid, although with less fish oil (10% vs 15%), demonstrated increased levels of fatty acids associated with reduced inflammation with the fish oil ILE but no difference in total bilirubin.⁵⁴

Five pediatric randomized studies⁵⁵⁻⁵⁹ assessed the safety of Clinoleic in preterm infants for a short period. Given the duration, these studies did not address changes in liver function in a meaningful way. However, Clinoleic was associated with improved antioxidant measures, with one study showing decreases in proinflammatory cytokines. One medium-term study (60 days) of children with stable liver function at trial enrollment did not demonstrate any adverse hepatic consequences with Clinoleic.⁶⁰ Trials comparing Clinoleic and SMOFlipid are ongoing.⁵¹ The hepatic outcomes from these studies will be of particular interest.

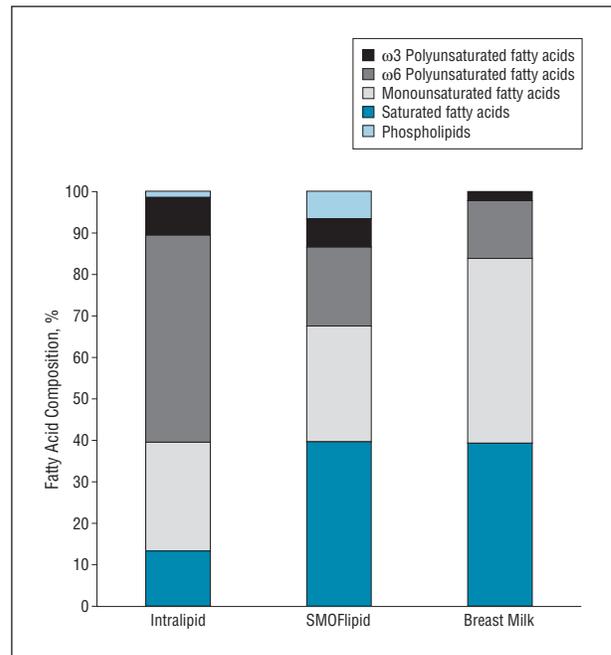


Figure. Fatty acid composition of Intralipid, SMOFlipid, and breast milk. Although Intralipid contains ω -3 fatty acids, it is all in the form of alpha-linolenic acid, which is not available for use by the infant because of immaturity of metabolic pathways. See the "Experience with SMOFlipid" subsection of the "Clinical Experience With ω -3-Containing ILEs" section for an explanation of SMOFlipid.

CURRENT STATUS OF NOVEL LIPID-BASED APPROACHES

Much of the data regarding the novel lipid-based approaches are in children with advanced IFALD. However, optimal clinical outcomes will likely be achieved by preventing the development of IFALD. Although on the basis of the available data it seems like the novel lipid-based approaches may be beneficial for the prevention of IFALD, it is important to recognize that they have not been formally evaluated in this setting, although clinical trials with this aim are ongoing.^{61,62} Therefore, we believe that although the novel approaches may be appropriate for those with advanced IFALD, given the dearth of alternative therapies in those with early or no liver disease, these approaches should only be used in the context of randomized controlled trials.⁶³ Our caution relates primarily to the lack of high-quality evidence for the efficacy of these approaches and the limited safety data, including an understanding of the effect on growth and development. This concern is further highlighted by a recent publication from our group showing that only 10% of infants receiving PN with a CB level of 2 mg/dL progressed to more advanced IFALD, defined as a serum CB level greater than 6.7 mg/dL.⁶⁴ Therefore, should the threshold for initiation of a novel lipid-based approach be set at 2 mg/dL, as is already occurring at some centers, only 10% of surgical infants treated with a novel approach would be expected to benefit relative to conventional management.

Quality of Evidence

It is essential to recognize that all published data on lipid minimization,^{17-19,21,22} Omegaven,^{30-34,36-42} and SMOFlipid⁴⁸⁻⁵⁰

in established IFALD are from retrospective or uncontrolled studies. Furthermore, although SMOFlipid and other alternate ILEs have been suggested on the basis of the randomized trials to be associated with improved hepatic outcomes, the patient populations in these studies were either normal preterm infants or children receiving home PN with stable liver function rather than patients with IF at high risk of progressive IFALD.

Uncontrolled studies are subject to both known and unknown confounders. As such, inferences about the potential efficacy of these therapies must be tempered by this fact. The most prevalent confounder in the setting of patients with IF is the degree of enteral support with weaning of the PN concomitant with the novel lipid-based therapy. However, in our experience, there was only a median 10% increase in enteral tolerance in our patients who responded to Omegaven. Resolution of advanced cholestasis in this setting based on our historical experience is highly unusual.^{34,35}

Uncontrolled studies also do not allow one to assign causality, which is a particular issue when one considers the effect of Omegaven. Omegaven, as it has been used in those with advanced IFALD, represents both an alternate lipid source and a form of lipid minimization. The lipid dose used by the group in Boston and most of the other publications was 1 g/kg daily, and the mean lipid dose in our cohort was 1.4 g/kg daily. These doses are substantially lower than those that typically used for parenteral lipids in infants and within the range of lipid intake that we regard as lipid minimization. Therefore, the beneficial effect of Omegaven may be related to a reduced lipid dose rather than a qualitative change in lipid source. The experience with SMOFlipid in advanced IFALD and the experience from the use of ω 3 lipids in animal models of IFALD argue against the effect of Omegaven as being only one of dose restriction. However, until data are available from clinical trials that control for both dose and source, this question remains unanswered. However, both Omegaven and SMOFlipid contain more alpha tocopherol than Intralipid, with this antioxidant being another potential confounder.

Safety Concerns

Concerns Related to Lipid Restriction. The long-term implications of reduced lipid dose on growth and development are unknown. Therefore, although dose restriction may be appropriate for the treatment of advanced liver disease, it may not be acceptable in the preventive setting. We believe that there needs to be a higher level of evidence in terms of long-term safety and efficacy before substantially altering recommended parenteral fat and energy intake in infants given, the critical role that lipids, including both ω -6FAs and ω -3FAs, play in neurodevelopment.⁶⁵

Reducing lipid intake also has the potential to result in essential fatty acid deficiency (EFAD). In the series by Cober and Teitelbaum¹⁷ of 32 patients treated with lipid minimization, biochemical evidence of EFAD was noted in 8. Although the group in Boston has reported on patients with biochemical evidence of EFAD as assessed by the triene-tetraene ratio, they have stated that clinically significant EFAD has not occurred in their patients tak-

ing Omegaven.³² Other groups have, however, noted this complication.⁴¹ Although de Meijer et al⁶⁶ may be correct asserting that the 0.1% to 0.7% linoleic acid content of Omegaven is sufficient to prevent EFAD, we maintain that further evidence is needed regarding the use of any ILE at a lipid dose of less than 1 g/kg daily during a prolonged period in developing infants, especially in those with minimal or no liver disease. This assertion is further highlighted by a recent study by Malone et al,⁶⁷ demonstrating marked abnormalities of essential fatty acid profiles in 10 children who received only Omegaven (1 g/kg daily) for greater than 3 months. The fact that these children had normal triene-tetraene ratios, which are typically regarded as diagnostic for EFAD, may challenge the validity of this marker in children with IF. However, the clinical significance of these findings requires further evaluation.

ω 3-Specific Concerns. The major theoretical concerns regarding an imbalance between ω -3FA and ω -6FA intake relate to the ability of ω -3FAs to downregulate arachidonic acid, which may result in growth suppression, immunosuppression, increased lipid peroxidation, and delayed hemostasis.^{68,69} Neonatal animal models have, however, not demonstrated impairment in bone composition or growth.⁷⁰ No significant complications associated with Omegaven use in children have been reported in either the Boston or Toronto experience. There is a case report of a burr cell hemolytic anemia in a child with IF treated with Omegaven that resolved after discontinuation of the treatment.⁷¹ Given that ω -3FAs are known to alter red blood cell membrane dynamics, it is likely that this adverse effect was related to Omegaven.⁷²

Another theoretical concern is increased hepatic fibrosis demonstrated in a rabbit model of IFALD.⁷³ One of the limitations in assessing this issue clinically is that liver biopsies are rarely performed in patients with IFALD, especially when the child is demonstrating biochemical evidence of resolution. However, in a report of 2 cases, Soden et al⁷⁴ demonstrated progressive fibrosis with Omegaven use despite biochemical normalization. In addition, although Omegaven may result in normalization of hyperbilirubinemia, a biochemical improvement in serum CB does not rule out ongoing liver injury contributing to progressive fibrosis.⁷⁵ It is therefore unclear whether the progressive fibrosis was related to the fact that the child continued to receive PN with ongoing liver injury, the progressive fibrosis was the result of healing of the injury inflicted before the start of Omegaven therapy, or fibrosis is a specific adverse consequence of treatment with Omegaven.

Despite the apparent safety of Omegaven, we maintain that further experience with this and other related emulsions, such as SMOFlipid, are needed to ensure that the preparations are not associated with rare but serious adverse events. This additional experience is especially important when one considers the use of emulsions in patients with no or early IFALD, in whom the risk-benefit ratio is different from those with advanced IFALD.

CONCLUSIONS

Novel lipid-based approaches seem to be promising for the management of IFALD. However, high-quality evidence

on which to base treatment recommendations is lacking, especially for the prevention of IFALD. Therefore, more research, including data from high-quality clinical trials, is needed to better evaluate the efficacy of these approaches before their adoption in children with early IFALD. Furthermore, additional safety parameters, including the effect on nutrition, essential fatty acid profiles, and long-term growth and development, must be addressed.

Accepted for Publication: December 20, 2011.

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Author Contributions: *Study concept and design:* Diamond. *Analysis and interpretation of data:* Diamond, Pencharz, Feldman, Ling, Moore, and Wales. *Drafting of the manuscript:* Diamond. *Critical revision of the manuscript for important intellectual content:* Diamond, Pencharz, Feldman, Ling, Moore, and Wales. *Study supervision:* Pencharz, Feldman, Ling, Moore, and Wales.

Financial Disclosure: The authors have received investigator-initiated trial funding from Fresenius Kabi, the manufacturer of both Omegaven and Intralipid, to evaluate SMOFlipid for the prevention of IFALD. Dr Diamond is the recipient of a Graduate Studentship Award from the Canadian Liver Foundation and the Chisholm Memorial Fellowship, Post Graduate Medical Education Office, University of Toronto. Dr Diamond was also supported by a fellowship award from the Canadian Institutes of Health Research, with additional support from the Surgeon Scientist Training Program, Department of Surgery, University of Toronto. Dr Feldman is supported by a Canada Research Chair in Childhood Arthritis.

Additional Contributions: The following members of the Group for Improvement of Intestinal Function and Treatment team, our multidisciplinary intestinal rehabilitation program, provided contributions to our experience with and understanding of IFALD: J. Darch, J. Brennan-Donnan, J. Bowers, M. Carricato, K. Cormier, G. Courtney-Martin, L. Coxson, N. D'Amato, M. De Angelis, N. de Silva, A. Fecteau, D. Fierheller, D. Grant, A. Gold, D. Harrison, J. Hawes, L. Ives-Baine, P. Kean, C. Kosar, C. Koziolok, K. Lang, J. Maxwell, K. Murch, C. Newman, V. Ng, C. Patterson, A. Rogers, M. Rugg, and S. So.

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