



## Review on hepatic explant pathology of pediatric intestinal transplant recipients: Is it time for an oil change?

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### Abstract

A recent study attempts to add to the body of evidence that is emerging regarding the fish oil parenteral lipid product Omegaven™. The authors have shown from explant livers of children on chronic parenteral nutrition with Omegaven™ that biochemical improvement in cholestasis does not always reflect improvement in liver histology. These findings support 2 small case series that were previously published. Despite improvement and resolution of hyperbilirubinemia in all six infants,

five of six infants had persistent or progressive hepatic fibrosis, while only one infant had regression of fibrosis. The study raises questions of whether there is a window of opportunity for efficacy of this preparation; also, an important question is if this omega-3 fatty acid-rich preparation is superior to newer "blended lipids" containing olive, coconut, soy, and fish oil.

**Key words:** Intralipid; Omegaven; Parenteral nutrition; Short bowel syndrome; Omega-3 fatty acid

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**Core tip:** Short bowel syndrome in infants frequently leads to intestinal failure. The use of soybean-based parenteral lipids allowed a major increase in parenteral calories but its use has been associated with development of severe liver disease. In the study by Matsumoto *et al*, six infants with liver failure secondary to parenteral nutrition experienced improvement and resolution of hyperbilirubinemia in response to a fish oil preparation, but when they came to liver/intestinal transplantation, 5 had persistent or worsening hepatic fibrosis. There may be other, better alternatives to Omegaven™.

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### INTRODUCTION

Matsumoto *et al*<sup>[1]</sup> recently published their observations on hepatic explant pathology of pediatric intestinal

transplant recipients. The study group evaluated explant livers at the time of intestinal transplantation in 7 children who received intravenous omega-3 fatty acids (O3FA) for a mean of 16 mo before transplant. Median total bilirubin fell from approximately 7 mg/dL (total) to 0 mg/dL at the time of transplant, a level which was significantly better than the comparative levels of a matched cohort of children on soybean-based omega-6 fatty acid lipids. However, all 7 of the O3FA-treated patients had advanced fibrosis (stage 3 or 4) on explant pathologic examination. Histologic inflammatory scores were marginally lower in the O3FA group with similar degrees of advanced fibrosis as in the soybean oil control group. The authors concluded that O3FA may have a limited role in preventing hepatic fibrosis associated with chronic parenteral nutrition.

## COMMENT

Short bowel syndrome is a relatively common, sometimes lethal, and highly costly medical problem in North America. Short bowel syndrome (SBS) frequently leads to intestinal failure, defined as inadequate intestinal absorption of nutrients, water and/or electrolytes, resulting in the inability to support health, growth and development and necessitating parenteral nutrition.

Traditionally, about 30% of parenteral calories have been provided by lipids. Wretling developed the first commercially available and relatively safe formulation called Intralipid fifty years ago<sup>[2]</sup>. This formulation was composed of soybean oil emulsified in an egg yolk-derived phospholipid layer to simulate enteral fat absorption. After introduction of this lipid formulation, numerous beneficial effects were noted, including improvements in hyperglycemia, hepatic steatosis, and essential fatty acid deficiency. Since then, other formulations of parenteral lipid have been developed, and most of these formulations are plant (soybean)-derived emulsions.

While use of parenteral lipid allowed significant improvement in morbidity and mortality in patients with intestinal failure, its use has been associated with development of severe and often life-threatening liver disease. Lipid overload syndrome was reported in infants receiving parenteral lipid at doses > 4 gm/kg.d, manifested by symptoms of elevated liver enzymes, hepatosplenomegaly, coagulopathy, and thrombocytopenia<sup>[3,4]</sup>. A higher incidence of cholestasis and liver fibrosis has subsequently been reported in patients chronically receiving parenteral lipid doses of > 2 gm/kg • d<sup>[5]</sup>.

The etiology of the potential toxic effect of parenteral lipids remains unclear. Some studies implicate a role of the omega-6 fatty acids, the major components of plant-derived lipid preparations, such as Intralipid. Omega-6 fatty acids are generally pro-inflammatory, and experts speculate that these

fatty acids also promote hepatic inflammation and injury. Recent evidence appears to implicate another component of soybean oil emulsions: phytosterols, which are plant-derived sterols similar in structure to cholesterol. Phytosterols cause a reduction of bile flow in animal models. Phytosterol levels are higher in cholestatic children, although it is not clear if this elevation is the cause or result of liver disease<sup>[6]</sup>. A key mechanism of injury has been established in animal models, in which a major sterol in soybean oil emulsion, stigmasterol, inhibits farnesoid X receptor (FXR) target genes<sup>[7]</sup>. FXR is the hepatocyte nuclear receptor for bile acids and mediates cytoprotection by suppressing bile acid uptake, decreasing bile acid synthesis, and enhancing bile acid secretion *via* the bile salt excretory protein<sup>[7]</sup>.

The recent study by Matsumoto *et al.*<sup>[1]</sup> reignites a controversial issue in management of pediatric intestinal failure. In 2006, Gura *et al.*<sup>[8]</sup> first reported a case series in which two infants with intestinal failure-associated liver disease had resolution of their cholestasis after their plant-based lipid emulsion was replaced with an omega-3-rich fish oil emulsion. Since then, a number of studies have revealed potential benefits of Omegaven<sup>™</sup>, a fish-oil based parenteral lipid formulation<sup>[9-11]</sup>. Several major centers have promoted aggressive use of this fish oil lipid emulsion despite limited and, arguably, controversial data. While subsequent studies have revealed a clear improvement of biochemical cholestasis with use of fish oil based lipid emulsions, infants receiving soy based lipids who were receiving higher doses of plant based lipids were subsequently placed on lower, lipid-restricted doses of Omegaven<sup>™</sup> of 1 g/kg/d. Different dosing strategies used for Omegaven<sup>™</sup> made it difficult to draw conclusions of Omegaven's<sup>™</sup> superiority over conventional lipid emulsions based on the available data.

A number of studies have attempted to address this controversy by using lipid modification strategies. Studies by Cober *et al.*<sup>[12]</sup> demonstrated improvement in biochemical evidence of cholestasis, with minimization of plant based lipid emulsions to doses similar to those used in infants receiving Omegaven. Sanchez *et al.*<sup>[13]</sup> employed a strategy of prophylactic restriction of soybean oil-based lipids in a group of surgical infants requiring parenteral nutrition for at least two weeks. When compared to a recent historical cohort, infants receiving low dose lipid were 1.8-fold less likely to develop cholestatic liver disease.

The Matsumoto *et al.*<sup>[1]</sup> study attempts to add to the body of evidence that is emerging regarding Omegaven<sup>™</sup>. The authors have again clearly shown an important observation with Omegaven<sup>™</sup> use, that biochemical improvement in cholestasis does not always reflect improvement in liver histology. Soden *et al.*<sup>[14]</sup> initially reported failure of resolution of portal fibrosis in two infants receiving Omegaven<sup>™</sup> despite improvement in cholestasis. Mercer *et al.*<sup>[15]</sup>

subsequently showed progression of hepatic fibrosis despite use of Omegaven™ in a series of 6 infants in whom serial liver biopsies were obtained. All but one of these infants were placed on fish oil lipid emulsion prior to three months of age. Despite improvement and resolution of cholestasis in all six infants, five of six infants had persistent or progressive hepatic fibrosis, while only one infant had regression of fibrosis. Similar findings of biochemical improvement without clinical improvement have been noted in treatment of other chronic cholestatic liver disorders, such as adult primary sclerosing cholangitis. As the authors have stated, further studies may be helpful including use of histology, but concerns over the increased risk of the biopsy in young, sick children as well as concerns of sampling error, complicate this approach.

Based on results of Matsumoto's study, one could argue that use of Omegaven™ should occur early in order to arrest the progression of liver disease, given that the authors did note that two infants who received Omegaven™ at an early age did not require rescue liver transplant with their intestinal transplant. Furthermore, the authors reported greater inflammatory changes in the omega-6 cohort vs the omega-3 cohort. While this may be true, there was no mention of dosing of lipid that infants received prior to Omegaven™ use. It is possible that lipid minimization whether it be in association with fish oil emulsions or plant-based emulsions may halt or reduce the progression of liver fibrosis. Recently, an attempt was made to address this controversy through a double-blind randomized controlled trial examining infants less than 3 mo of age receiving either 1 g/kg of either a fish oil-based intravenous fat emulsion or soybean oil-based fat emulsion<sup>[16]</sup>. Eligibility required that baseline bilirubin be lower than 1.0 mg/dL. After no differences were noted in growth, coagulopathy, infectious complications, hypertriglyceridemia, or adverse neurodevelopmental outcomes, the study resulted in early termination, because the incidence of cholestasis in both treatment arms was lower than expected.

The European approach to this problem has been to adopt an emulsion containing a mixture of soy oil (30%), coconut oil (30%), olive oil (25%), and fish oil (15%). This preparation is called SMOF-lipid (Fresenius Kabi, Bad Homburg, Germany). This combination boasts of combining oils rich in monosaturated fatty acids (FA's) (olive oil), oils rich in omega-6 FA's (soybean oil), those rich in omega-3 FA's (fish oil), and those rich in medium chain triglyceride (coconut oil). The gamma-tocopherol in soybean oil has some antioxidant characteristics, but less than the vitamin E in Omegavyn™. The SMOF-lipid is said to deliver a product that may not only prevent liver toxicity but also may optimize growth<sup>[17]</sup>. Again, no randomized trials have compared SMOF-oil with Omegaven™, but both appear to be associated with excellent results.

## CONCLUSION

There are 3 approaches to reducing the incidents of parenteral nutrition-associated cholestasis: lipid minimization, administering only omega-3-rich lipids, and using a composite lipid preparation. A recent position paper on lipid formulation by the American Society of Enteral and Parenteral Nutrition stresses the need to define the ideal mixture of parenteral lipid and the role of fish oil in management of chronic conditions such as intestinal failure<sup>[18]</sup>. We agree that long term studies may be helpful in addressing not only the obvious concerns regarding liver toxicity but additionally the potential long-term nutritional effects of these lipid modification strategies.

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