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Compassionate Use of a Fish Oil-derived Intravenous Fat Emulsion (Omegaven®) to Reverse Parenteral Nutrition (PN) Induced Cholestasis

Cincinnati Children's Hospital Medical Center
Research Protocol

Title: Compassionate Use of a Fish Oil-derived Intravenous Fat Emulsion (Omegaven®) to Reverse Parenteral Nutrition (PN) Induced Cholestasis

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I. Abstract

Infants with intestinal failure require chronic administration of parenteral nutrition (TPN). The population under one year of age on TPN is at greatest risk for parenteral nutrition associated cholestasis (PNAC), but, even among older individuals on TPN, the emergence of cholestasis carries a bad prognosis. A number of factors play a role in PNAC. These include endotoxemia, prolonged fasting, immaturity of bile secretory mechanisms among infants, intravenous infusion of high glucose concentrations, intravenous infusion of high protein loads, and intravenous infusions of soy based lipid emulsions. Human data reveal that TPN administered to infants for over three weeks is associated with PNAC. Further analysis reveals that cholestasis is closely associated with the administration of soy-based lipids which contain potentially hepatotoxic phytosterols. Thus lipid reduction strategies have been employed for reversal of PNAC. They sometimes work, but put infants at risk for essential fatty acid deficiency. An alternative strategy of providing lipid in the form of Omegaven®, a fish oil-derived emulsion, is extremely promising, and has been used successfully with virtually no complications in an uncontrolled trial at Boston Children's Hospital. Ongoing controlled studies of Omegaven® are underway at Boston Children's Hospital, and several other institutions have published small case series or case reports suggesting that Omegaven® is effective and safe. It is not FDA approved because none of the ongoing placebo controlled trials have been completed yet in the United States, but, because of its anti-inflammatory properties, it is approved in several European countries for use in adults with inflammatory conditions. Every year, we observe several children in our own practice who have no hope of coming off TPN for several months and who have progressive cholestasis. Our own unpublished data suggest that once PNAC has been established in the absence of endotoxemia, it is usually reversible. However, this may not be true if less than approximately 70% of daily calories are derived enterally. We also have published data in abstract form suggesting that a high conjugated bilirubin to gamma GT ratio is a poor prognostic sign. This study provides Omegaven® for compassionate release to those infants within our practice who have developed progressive cholestasis despite reduction in parenteral lipid below one gram per kilogram

body weight per day, and who are unlikely to tolerate substantial enteral nutrition until several months following their small intestinal insult.

II. Purpose of Study

The specific aim of this study is to ascertain whether PNAC can be reversed if a fish oil-based intravenous lipid product (Omegaven®) at a dose of up to 1 g/kg body weight/day is substituted for a soy-based intravenous lipid product (Liposyn® or Intralipid®) as part of the daily TPN of infants and children with intestinal failure and PNAC. Secondary aims will be to confirm the safety of Omegaven®.

III. Background

In North America, infants and children who require parenteral nutrition (TPN) customarily receive solutions whose caloric distribution is balanced between glucose, protein, and fat to provide approximately 60-70 % of calories via glucose, 10-15 % of calories via protein, and 20-30% of calories via lipid.(1) Commercial lipid solutions utilized in North America are customarily soy-based, and contain high quantities of phytosterols including sitosterol and stigmasterol. Animal data suggest that high quantities of stigmasterol inhibit fxr, a nuclear receptor in the hepatocyte that helps to regulate bile acid homeostasis by controlling expression of bile acid export pumps. (2) Thus, exposure to a high quantity of stigmasterol is potentially hepatotoxic to individuals who have a propensity for cholestasis due to a poorly developed bile secretory process.

It is known that infants and children with underlying intestinal failure are at extraordinarily high risk for cholestasis. (3). The cholestatic process is reversible in approximately ¾ of infants with parenteral nutrition associated cholestasis (PNAC), even when soy-based lipid emulsions are given parenterally, if those infants can experience small intestinal adaptation and ultimately tolerate and assimilate the majority of their calories via enteral nutrition. Unfortunately, if adaptation does not occur rapidly enough, PNAC may progress to endstage liver disease resulting in death or necessitating combined liver/small intestinal transplantation.

A popular strategy for minimizing the toxicity of lipid emulsions is to reduce the amount of lipid in parenteral nutrition to between 0.5 g/kg body weigh/day and 1g/kg body weight/day. (4) Preliminary results suggest that this strategy is beneficial for some infants, but that it is not universally effective. One potential reason for lack of effectiveness among some cholestatic infants is that endotoxemia is commonplace in children with intestinal failure receiving TPN, and that stigmasterol potentiates the cholestatic effect of endotoxin upon the liver. Therefore, when the infant with a cholestatic propensity is exposed to endotoxin and even modest quantities of stigmasterol, cholestasis could progress.

An alternative liver-protective strategy for children on TPN has been to provide all of the patients' parenteral lipid in the form of a fish-oil based product called Omegaven®. (5) This product has been used for over 10 years as an adjunct to conventional fat emulsions.

According to current data, an increase in the proportion of omega-3 fatty acids is thought to optimize nutrition in general, but in particular benefit patients whose underlying disease might benefit from an increase in omega-3 fatty acids. An adequate intake of omega-3 fatty acids results in anti-inflammatory and immunomodulatory effects that are protective against inflammatory tissue damage and capillary permeability. In addition, adults on Omegaven® seem to display improved immunological resistance. Omegaven® may also reduce the risk of thrombosis and increase microvascular perfusion due to its anti-aggregatory and vasodilatory effects.

In Europe and Asia, parenteral omega-3 fatty acids have been used in the following adult patient populations:

1. post traumatic and post surgical patients
2. patients experiencing early stages of sepsis/SIRS
3. patients at risk of hyperinflammatory processes
4. patients with inflammatory bowel disease (Crohn's disease, ulcerative colitis)
5. patients with inflammatory skin diseases (psoriasis, atopic eczema)

The dosing used in these patients was 0.1 (1ml) to a maximum of 0.2 g (2ml) /kg body weight. The infusion rate used did not exceed 0.5ml/kg/body weight/hour. Since it was intended to be infused in combination with conventional fat emulsions, the total fat intake was limited to 10-20% as fish oil. The duration of administration did not exceed 4 weeks.

Two non-North American trials suggest that Omegaven® is safe when administered to young children. (6,7) These trials were performed in Germany and Taiwan. The German study was a controlled, randomized, open parallel-group clinical study to investigate whether or not omega-3 fatty acids could be incorporated into the plasma phospholipids of very low birth weight preterm infants. In this 7-day safety trial, Omegaven® use was evaluated on the basis of clinical, laboratory, and antioxidant parameters and lipid metabolism. Treatment was started on day 3-5 of life and continued for a total of 7 days. Patients received Omegaven® plus conventional soybean fat emulsion or soybean emulsion alone. The maximum dose of Omegaven® in the study was 0.2 gm/kg/day. The study concluded that the Omegaven® was well tolerated in this group of preterm infants in respect to both hematological and biochemical parameters. The incidence of reported adverse events between both study groups was similar. The eicosapentaenoic acid (EPA) content of plasma phospholipids increased significantly in the Omegaven® arm, with the proportion of EPA to the total fatty acids reaching almost three times the baseline value. The sum of omega-3 fatty acids showed a significantly greater increase in the Omegaven® group compared to the conventional treatment arm.

The Taiwanese study was a single center, controlled, open-labeled study conducted to investigate the safety of parenteral administration of Omegaven® in preterm infants. The group of 20 infants were randomized to one of two treatment groups; one consisting of Omegaven®/conventional lipids and the other consisting of conventional lipids alone. The average dose of Omegaven® in the treatment group of this 14-day study was 0.13 ± 0.02 g/kg/day. There were no significant differences between the two groups with regard

to body weight and length. Similarly, there was no significant difference in the hematological or biochemical parameters. There were no adverse events that were attributable to Omegaven® use. It was concluded that Omegaven® was well tolerated in these preterm infants.

While non-North American studies conclude that Omegaven® is safe and that it may have anti-inflammatory properties, they do not address a potential liver protective effect for the agent. Data from North America suggest a salutary role for Omegaven® in PNAC. The group at Boston Children's hospital had initially utilized Omegaven® in a child with soy allergy who required TPN. (8) Subsequently, they reported upon two children who received Omegaven ® for PNAC, demonstrating that cholestasis resolved in both and that neither of them experienced side effects. (9). A subsequent open label trial performed at Boston Children's Hospital showed both safety and resolution of cholestasis in 18 children with advanced PNAC.(5) Historical controls receiving soy-based lipid emulsions showed progression of cholestasis rather than resolution. Currently, a double blind, controlled study comparing 1 g/kg body weight/day of Omegaven® with 1 g/kg body weight/day of Intralipid® is being conducted in Boston, and results are quite promising (Kathleen Gura, personal communication). Many other pediatric institutions, including our own, have utilized Omegaven® to treat PNAC. This agent is available in over 30 institutions, and no significant adverse effects have been reported. Small case series and case reports have been published confirming safety and suggesting effectiveness for PNAC (10).

Our own experience with Omegaven® is confined to three patients. The first was a 2 year-old who underwent an extensive intestinal resection for a stage 4 neuroblastoma with CNS metastases at another institution. In an attempt to resect her primary retroperitoneal abdominal neuroblastoma, an intraoperative vascular catastrophe occurred, resulting in loss of all of her small bowel except for a small duodenal stump which was oversewn. Therefore, her esophagus, stomach, and proximal duodenum were a blind loop, and she could receive no enteral nutrition whatsoever. Her conjugated bilirubin had risen to approximately 6 mg/dl, and her parents took her to Boston Children's Hospital where Omegaven® was started. She also underwent chemotherapy for her neuroblastoma, and while she was tumor-free, her bilirubin normalized despite absence of enteral alimentation and prolonged use of TPN. Only when her tumor recurred and she developed hepatic metastases did her bilirubin once again climb to an abnormally high level. Figure 1 shows her conjugated bilirubin plotted against time. Her platelet counts remained below normal because of bone marrow suppression due to chemotherapy, but following each course of chemotherapy, they rose to between 70,000 and 120,000 u/L until her next course of chemotherapy. We did not have our own protocol in place to offer Omegaven®, but our pharmacy dispensed Omegaven® which had been obtained from Boston Children's Hospital when she was an inpatient here at CCHMC.

Our second patient was a 14 month old ex 29 week gestation premature infant who developed severe necrotizing enterocolitis requiring surgery. He underwent two separate bowel resections, and was left with 27 cm of jejunum beyond the ligament of Trietz. He

was feed by continuous feedings of an elemental formula, and his feedings were slowly being advanced while he concomitantly received parenteral nutrition. His conjugated bilirubin level remained approximately 3 mg/dl until he developed Klebsiella sepsis with shock and multi-organ failure. This septic event left him with significant neurologic impairment as well as worsened hepatic and pulmonary function. His conjugated bilirubin abruptly climbed to approximately 30 mg/dl, and his hepatic synthetic function deteriorated. He required mechanical ventilation. We then obtained Omegaven® by compassionate release after approval by the CCHMC IRB (protocol # 2009-1041). Omegaven® was administered for approximately 4 weeks and Figure 2 demonstrates the progressive fall in his conjugated serum bilirubin. Unfortunately, he developed progressive respiratory failure and expired in early September of 2009 despite improving hepatic function. He experienced neither worsening of platelet count nor signs of essential fatty acid deficiency while he was on Omegaven®.

Our third patient was a 26 week gestation ex premature male who developed severe necrotizing enterocolitis during his first week of life. He required an extensive small bowel resection, and was left with approximately 40 cm of jejunum beyond the ligament of Trietz. His surgery was complicated by an enterocutaneous fistula which engendered a delay in initiating feedings. He received no more that trophic feedings of Elecare® at a rate of 2 ml/hour. He was allowed to drink no more than 5 ml of formula two times daily. His fistula was closed on November 5, 2009, but he could not tolerate full enteral feedings for approximately 16 weeks later. Meanwhile, he received virtually all of his nutrition via TPN. He developed parenteral nutrition associated cholestasis (PNAC) by his second week of life, and his conjugated bilirubin levels progressively increased while his GGT levels fell. He was started on Omegaven® when his conjugated bilirubin level had risen above 2 mg/dl and persisted between 2 mg/dl and 4 mg/dl for approximately six weeks. He was started on 1 g/kg/day of Omegaven® at the same time that feedings were started. His bilirubin fell to <2 mg/dl within 10 days while his enteral intake constituted only 30% of his total caloric intake. He is now on full enteral feedings with a normal conjugated bilirubin level. Levels of his conjugated bilirubin are demonstrated in figure 3.

PNAC is a potentially fatal disorder, and the consequences are heinous if the process cannot be reversed. In Omegaven® we have an agent that is potentially life saving, and its use in hundreds of patients has shown little if any toxicity. After ongoing controlled trials of Omegaven® are completed, the agent will be evaluated for approval by the FDA. Until such time as FDA approval is granted, we will be unable to administer Omegaven® without requesting approval for compassionate use. The IRB granted approval for protocol 2009-1041, and this protocol will call for even stricter inclusion criteria. Therefore, we seek IRB approval for this study.

IV. Duration of Study

Once IRB approved, enrollment of subjects into this study will occur for up to 9years. Subjects will receive Omegaven at a dose of up to 1 g/kg body weight/day until they no

longer require TPN or until their conjugated or direct bilirubin has normalized and their enteral lipid intake is sufficient to discontinue intravenous lipids.

A total study duration of 10 years is anticipated to complete the study (enrollment, analyses, and report writing).

V. Potential Benefits

The use of Omegaven® has the potential to benefit patients with PNAC by facilitating the resolution of cholestasis.

VI. Potential Risks of Omegaven® Treatment

Omegaven® has been studied in animal pre-clinical models as well as Phase I, II, III, and post marketing human trials in both Europe and Asia. Prolonged bleeding time and an inhibited platelet aggregation can occur. It should not be administered to patients known to be allergic to fish or egg protein.

Contraindications to Omegaven® include the following**:**
1. Impaired lipid metabolism
2. Severe hemorrhagic disorders
3. Unstable diabetes mellitus
4. Collapse and shock
5. Stroke/Embolism
6. Recent cardiac infarction
7. Undefined coma status

Side Effects:
Risks of Omegaven®
The infusion of Omegaven® can lead to a prolonged bleeding time and an inhibited platelet aggregation. In rare cases, patients may experience a fishy taste.
The administration of Omegaven® should be stopped or reduced if there is a marked increased in blood glucose levels during the Omegaven® infusion. Undesirable effects that are seen during the infusion of Omegaven® that may also occur with conventional fat emulsions (i.e., Liposyn® or Intralipid®) include:

1. Slight rise in body temperature
2. Heat sensation and/or cold sensation
3. Chills
4. Flushing or cyanosis
5. Lack of appetite, nausea, vomiting
6. Dyspnea
7. Headache, pain in the chest, bone pain
8. Priapism
9. Increase/decrease blood pressure
10. Anaphylactic reactions/erythema

Risks for blood draw:

- Occurrence of discomfort and/or a bruise at the site of puncture
- Less commonly, fainting
- The formation of a clot or swelling in the vein and surrounding tissue
- Bleeding from the puncture site
- On rare occasions an infection may develop at the site where the blood is collected

Potential Risks of No Treatment

Since Omegaven® will only be offered to those patients for whom no standard therapy has been safe and effective, the risks of not being treated are those allowing for the natural history of their disease and associated clinical manifestations to progress. These include fulminate liver failure and death.

VII. Overall Risk Assessment

Patients will be at some risk inherent in taking a pharmaceutical agent that has not been fully evaluated for long duration treatment. However, the availability of safety data demonstrates no life-threatening risks or toxicities to vital organs or physiologic functions. The potential benefits of Omegaven® in this patient population are mainly based on human trials and our own experience.

VIII. Risk Category

The research involves greater than minimal risk, but presents the prospect of direct benefit to the individual subjects.

IX. Methods

A. Subject Selection

No concomitant medications will prohibit enrollment.

Inclusion Criteria

1. Males and females ages one month of age to 18 years of age
2. Patients with intestinal failure on TPN
3. Patients who have a conjugated or direct bilirubin of ≥3 mg/dl for more than 4 weeks and in whom other causes of cholestasis have been excluded with reasonable certainty utilizing biochemical, serologic, microbiologic, and radiographic techniques. Liver biopsy is not required to rule out other disorders, but may be utilized at the clinician's discretion
4. Patients in whom reduction of IV soy-based lipid load to an **average** <1.2g/kg body weight/day has failed to reduce the conjugated or direct bilirubin within ≥ 30 days of implementation

5. Willing to use birth control during study participation for females of child-bearing potential, as determined by investigator.
6. Signed informed consent for use of Omegaven® obtained

Exclusion Criteria

1. Any of the contraindications to use of Omegaven®
    - Impaired lipid metabolism (triglycerides >1000 mg/dL) while on 1g/kg/day or less of Intralipid
    - History of severe hemorrhagic disorders (ie. hemophilia, Von Willebrand disease, etc.)
    - Unstable diabetes mellitus
    - Collapse and shock
    - Stroke/ Embolism
    - Cardiac infarction within the last 3 months
    - Undefined coma status
    - Pregnancy (positive pregnancy test) prior to enrollment in the study for females of child-bearing potential
    - Females of child-bearing potential who are unwilling to use birth control during study participation
2. Parental decision to forego the use of Omegaven®
3. Known fish or egg allergy
4. Pregnancy
5. Causes of liver disease other than PNAC

B. Withdrawal Criteria

1. Decision of an assenting minor/adult subject or parent/guardian to withdraw from the study*
2. Anaphylaxis
3. Evidence of spur cell anemia.
4. Increasing anemia (hemoglobin < 7 g/dL) in the absence of gastrointestinal bleeding.
5. Mucosal bleeding or bleeding from IV insertion sites requiring transfusion.
6. Reproducible priapism associated temporally with the infusion
7. Mucosal bleeding associated with abnormal platelet function
8. Bowel adaptation such that patient can either come off TPN or such that enteral fat can meet the patient's nutritional requirements
9. Patient undergoes liver transplantation
10. Pregnancy
11. Patient is lost to follow up

* If an assenting minor chooses to withdraw from the study early, even if the parent wants the child to participate, the child will have their wishes respected.

C. Stopping Rules

If two subjects develop the same grade-3 adverse event (including liver function tests,

coagulation profile, and platelet count) related to the study medication that is irreversible upon de-escalation (does not reverse after 10 days) or upon discontinuation of the study drug, or any subject develops a related grade-4 adverse event, these events will be the cause for termination of the study.

D. Monitoring for toxicity due to Omegaven®

Potential toxicity will be assessed by analyzing clinical and laboratory parameters including serum electrolytes, hematological studies, serum triglycerides, total cholesterol, liver function tests, and essential fatty acid profiles where applicable. Blood samples will be taken in accordance with current institutional standards for monitoring hyperalimentation. In the face of mucosal bleeding, studies of platelet function (closure time) will also be performed.

E. Patient Recruitment and Consenting Process

Patient Recruitment

Approximately 25 patients, ages one month to 18 years will be enrolled from Cincinnati Children's Hospital. All patients will be enrolled as inpatients. The study will be explained in detail by the physician and study coordinator and the consent form (and age appropriate assent forms) will be reviewed per institutional IRB requirements. These subjects will be recruited through the Division of Gastroenterology, Hepatology, and Nutrition, the Department of Surgery, or the Division of Neonatology. The prospective patients will be identified through the clinical staff within all three divisions working collaboratively. The clinical staff will initially inform potential subjects and families about the research study. The research staff will notify and obtain permission from the patient's primary gastroenterologist, surgeon, or neonatologist before contacting the family.

Subjects who drop out prior to drug initiation may be replaced with new subjects until target enrollment is achieved, as these will not have been given study medication.

Consenting Process

For those patients meeting inclusion criteria, the study purpose, procedures, costs, risks, benefits, and alternatives to participation will be thoroughly explained and presented to the patient and their family by the designated study coordinator and/or investigator, and subjects will be screened for willingness to participate. Subjects and parents will be explicitly informed that choosing not to participate will in no way affect the quality of the medical care that they will receive. Once patients and families have had enough time to consider participation and have expressed a willingness to participate, informed consent will be obtained from the parents or legal guardian and child assent when appropriate based on age and institutional IRB requirements.

Due to the age of the subjects, an age appropriate assent form will be reviewed with children who are 11 to 17 years of age. The PI and/or study coordinator will review the

consent with the parent/guardian, giving them time to ask questions and discuss concerns with the investigator. Minors who age 11 to 17 years old will also be given an age appropriate assent form for their review to make certain they understand the study goals and procedures. After everyone is comfortable with the study and procedures and the family has agreed to participate, the family will sign the parental permission form and (if applicable) the assent form.

If a subject is 18 years of age at the time of enrollment, they will be consented as an adult and parental permission will not be required. Any subject who turns 18 during the course of the study will be asked to provide informed consent as an adult.

One copy of each consent/assent will be given to the family and one will be retained in the study records. One copy will also be placed in the child's medical record.

Vulnerable Population

This study will enroll children and adolescents. To protect this population from coercion or undue influence, informed consent will be obtained only after a full discussion of the research protocol and of the risks and benefits that may occur from participation. Patients and parents will be explicitly informed that choosing not to participate will in no way affect the quality of the medical care that they will receive.

Due to the age of subjects, an age appropriate assent form will be reviewed with children over the age of eleven. The PI and/or study coordinator will review the consent with the parent/guardian, giving them time to ask questions and discuss concerns with the investigator. Minors who are 11 years old or older will also be given an age appropriate assent form for their review to make certain they understand the study goals and procedures. After everyone is comfortable with the study and procedures and the family has agreed to participate, the family will sign the parental permission form and (if applicable) the assent form. If an assenting minor chooses not to participate, even if the parent wants the child to participate, the child will have their wishes respected.

F. Study Procedures

The following will take place at study visits:

At the screening visit (Day 0):

- Informed consent/assent
- Screening for eligibility, including:
    - Chart review

For those determined to be eligible, the following will occur:

- Complete medical history and physical exam
- Baseline Blood Tests including:
    - TPN panel
        - Liver profile
        - Renal profile

        - Ca
        - P04
        - Mg
        - Triglycerides
    - Essential fatty acid levels
    - Thromboelastography (TEG) - with platelet mapping preferred
    - CBC, differential, platelets.
    - PT/PTT (at outset and then monthly)
    - Cholesterol
- Pregnancy test (urine) for females of child-bearing potential.

All patients will be followed as inpatients within the Regional Center for Neonatal Care (RCNC), the Department of Surgery, and the Division of Gastroenterology. As outpatients they will be followed within the Comprehensive Nutrition Clinic (CNC). Laboratory monitoring of patients with intestinal failure on TPN can be found on Compliance 360. Inpatients undergo the same monitoring, but a TPN panel and CBC are performed once weekly. Outpatients will undergo weekly monitoring of vital signs and fluid balance as well as inspection of gastrostomies, enterostomies, and central venous catheter exit sites by home healthcare nurses.

While they are on Omegaven® they will be seen and examined twice a month for study visits, and they will undergo blood sampling twice a month to obtain repeat levels of their baseline tests for the first 6 months. After the first 6 months, they will be seen and examined monthly and will undergo monthly blood sampling. Adverse events and concomitant medication information will be collected and documented at each study visit.

Below is a description of the study procedures:

Medical History and Physical

A complete, comprehensive history and physical will be performed at the beginning and end of the study. An interim medical history and a brief physical exam will be performed at all other study visits.

Clinical and demographic data will also be obtained to include: age, gender, race, and current medications.

At other study visits, an abbreviated physical exam will be performed and changes in medical history or concomitant medications will be noted.

Phone Calls:

For the first 6 months of the study, a study coordinator will contact research participants/families weekly to assess for any changes in health status and changes to medications. Thereafter, the coordinator will contact participants/ families monthly

approximately midway between monthly clinic visits. Changes in clinical status and concomitant medications will be monitored until the end of the study.

Contact will occur by telephone unless subjects are seen in the clinic or are hospitalized. Applicable clinical records obtained at clinic visits and during hospitalizations such as H&Ps, labs, and medications can be used for research purposes.

Treatment with Investigational Drug

For the first two days of treatment, subjects will receive Omegaven® at 0.5 g/kg per day to assess tolerance and will progress to a maintenance dosage range of0.8 to 1.2 g/kg/day over 12 hours at an infusion rate approximating 1 g/kg/12 hours (10 ml/kg/12 hours). The 12-hour infusion time will be used to minimize waste because of Centers for Disease Control and Prevention requirements that source containers of lipid emulsion be changed every 12 hours. Dosing is based on previously described dosing of fish-oil emulsions as monotherapy noted within the literature (8). Omegaven® will be infused intravenously through either a central or peripheral catheter in conjunction with other parenteral nutrition containing dextrose and amino acids. Omegaven® is isotonic. It is compatible with parenteral nutrition solutions and may be co-infused via y-site.

While hospitalized, serum triglyceride levels will be monitored weekly to insure that triglyceride concentrations do not exceed 1000 mg/dl during the infusion of fat emulsion. During hospitalization, coagulation studies will also be conducted weekly. PT and PTT will be conducted at baseline and then monthly. Other laboratory tests will be conducted to monitor for blood glucose metabolism, electrolyte and fluid balance and liver and kidney function in accordance with current institutional standards for monitoring hyperalimentation. Thromboelastography (prefer with platelet mapping) will be obtained at baseline and approximately 10 days prior to scheduled surgery to access platelet aggregation dysfunction.

Urine pregnancy tests will be performed at baseline and monthly thereafter for females of child-bearing potential.

The patient will be observed for signs of metabolic overload and other adverse events. Adverse events will be documented by the study staff and may be used as a rationale for dosage adjustments of the study drug.

Study Drug Administration

While patients are inpatients, the study drug will be administered by the CCHMC pharmacy. After patients have been discharged, the drug will be administered by Cincinnati Children's Hospital Home Care Pharmacy and/or the family. The study drug may be delivered by the Children's Hospital Home Care Service just as Intraplipid® is currently delivered or provided by the study team at the participants' outpatient appointments.

Dose Reduction:

If hypertriglyceridemia develops, operationally defined as serum triglyceride levels >1000 mg/dL, after a patient has been enrolled in the study, the following will be considered prior to reducing the dose:

1. If the level was obtained while the patient was receiving a continuous 12-hour infusion of Omegaven®, a repeat serum triglyceride level will be obtained while the patient is off the infusion just prior to resuming the infusion.
2. Other sources of hypertriglyceridemia should be considered and addressed.

If the triglycerides continue to remain high after considering the above interventions, a dosage reduction of 25% should be considered. The rationale for a twenty five percent reduction is to offer a reasonable possibility for improvement in triglyceride levels while maintaining a lipid dose high enough to prevent essential fatty acid deficiency. Persistently elevated triglyceride values above 1000 mg/dl after 72 hours of a 25% dose reduction will result in a further 25% reduction. This process will be repeated every 72 hours until either the triglyceride levels have fallen below 1000 mg/dl or Omegaven® is stopped.

The rationale for operationally defining hypertriglyceridemia at a much higher level (>1000 mg/dl) than customarily defined (>200 mg/dl) is that levels of 200 to 1000 are commonplace among patients on TPN and intravenous lipid. These levels, while abnormal, are customarily secondary to cholestasis rather than being secondary to lipoprotein lipase deficiency, metabolic syndrome, or other causes of hypertriglyceridemia. We have chosen to make 1000 mg/dl our cut off because it is the level wherein serious complications such as pancreatitis and lipid overload syndrome may occur mandating immediate lipid reduction.

Follow-Up Assessments

(See Study Treatment Procedures Table below)

Following completion of the study medication, subjects will be seen for a final study visit within1 month for a follow-up assessment. A complete, comprehensive history and physical will be performed. Blood samples will be collected and a urine pregnancy test will be done for females of childbearing potential. Adverse events and concomitant medications will be documented by the study staff.

The following table summarizes Study Procedures:

Study Procedures Table

	Baseline (Day 0)	Weekly while Inpatient	Weekly for first 6 months	Twice a month for the first 6 months	Monthly	Final Visit (within 1 month after treatment)
Signed informed consent/assent	X					
History	X			X	X	X
Physical Exam	X	X		X	X	X
Blood specimen (4.4 mcl using microtainers)#	X	X		X	X	X
Urine pregnancy test*	X				X	X
Phone calls (clinical status and concomitant medication collection)			X		X **	

At baseline and then monthly for PT/PTT. At baseline and then weekly for other laboratory studies (see Section IX, E).
* For females of child-bearing potential.
** Phone calls will take place monthly (between the monthly visits)

G. Data Collection

Demographic and clinical information will be collected whenever clinical data are available via uniform baseline and follow up clinical data extraction forms to ensure accuracy and consistency. The essential demographic information includes age at diagnosis, gender, race and ethnicity, birth history, past medical history, and family history. The clinical information includes presence or absence of jaundice, hepatosplenomegaly, or ascites.

H. Compensation

Participants will not be compensated for study participation. Subjects will receive study medication, clinical supplies, and laboratory evaluations that are obtained outside the standard of care free of charge.

I. Withdrawal

Data collected from patients who withdraw from the study will be included in the final analysis using intent to treat. Patient enrollment will continue until all 25 patients complete all requested study requirements outlined. It will be recommended that patients withdrawn from the protocol resume a reduced lipid intake, treat infections promptly as they occur and advance feedings as quickly as tolerated.

X. Assessment of Efficacy

The primary endpoint will be reduction in conjugated or direct bilirubin level to below 1 mg/dl. Data from previous retrospective analyses and prospective uncontrolled studies suggest that from the inception of Omegaven® therapy, conjugated or direct bilirubin will remain elevated for approximately 8 weeks at levels comparable to those observed prior to administration of Omegaven®. Subsequently, levels are expected to fall by approximately 1 mg/dl/week until they normalize. The time to normalization will vary according to each patient's baseline conjugated or direct bilirubin level. Thus, a patient who begins Omegaven® with a conjugated or direct bilirubin level of 7 mg/dl is likely to experience normalization within 14 weeks (8+6 weeks). We will compare the group receiving Omegaven® with historical controls from our internal registry who have demonstrated cholestasis while on Intralipid®. We will compare changes in conjugated/direct bilirubin concentration over time between groups via Kaplan-Meier analysis (see Statistics section XIII).

Secondary endpoints will be: normalization of total bilirubin and liver enzymes. Differences in these values at the end of 14 weeks of therapy will be compared with those of controls via Kaplan-Meier analysis identical to that employed for conjugated and direct bilirubin levels. Furthermore, we expect that elevated triglyceride levels which might be present at the initiation of therapy will have normalized at the same time that liver profiles have normalized.

XI. Assessment of Safety/Data Safety Monitoring Board

A DSMB will monitor the study for the occurrence of adverse events (both serious and otherwise). A significant increase in the rate of adverse events would be cause for concern for the safety of participants in the study. Information on adverse events will be presented in several ways: (1) listings of serious adverse events with accompanying narrative summary by the PI: (2) summaries of adverse events by body system and type of event. This information will be presented to the DSMB.

The DSMB will also monitor the efficacy and the conduct of the study. Interim monitoring reports for the DSMB will include, but will not be limited to, such tabulations as:

1. platelet counts
2. essential fatty acid profiles
3. coagulation studies
4. liver profiles

5. renal profiles

The DSMB will meet at least once per year and possibly more frequently given the expected speed of recruitment and study medication administration.

The DSMB chair (or designee) will be asked to review SAE reports within 7 days after initial receipt of the information by the investigator(s), to review the PIs assignment of SAEs as related or unrelated to treatment, to confirm the grading of any toxicities and assure that they do not meet stopping criteria.

A safety analysis will be performed after approximately 5 patients have received 4 weeks of treatment or, if enrollment begins slowly, 12 months after the first patient is enrolled. Safety data will be shared with the Data and Safety Monitoring Board (DSMB). There will be no further enrollment until the DSMB makes recommendations. An investigator in this study may not be a member of the DSMB. Members of the DSMB will receive safety data approximately every 2 to 3 months for review. Safety assessments will consist of vital signs, AEs, and laboratory evaluations. A cumulative listing of patient withdrawals, dose adjustments, and serious adverse events (SAEs) will also be reviewed. DSMB members will be notified of all SAEs reported expeditiously to regulatory authorities.

Study Monitoring

The Translational Research Trials Office (TRTO) will act as the independent monitor for the study. Routine monitoring visits shall occur one or more times during the period after study initiation but before study closeout. Guidelines for scheduling monitoring visits shall be determined according to the development, complexity of the study, the rate of subject accrual and other factors. Monitoring visits are conducted for routine monitoring only and are intended to ensure that the protocol and applicable regulatory requirements are being followed, that subjects' rights and safety are protected, and to confirm data integrity and quality.

XII. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient participating in this trial. An adverse event can be an unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

A serious adverse event (SAE) is one that:

1. results in death
2. is life threatening
3. requires an inpatient hospitalization or prolonged a hospitalization
4. is disabling

5. is a congenital anomaly/birth defect
6. is an event that dose not meet the above criteria but may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

IRB Notification of SAEs

Per CCHMC Institutional Review Board (IRB) Requirements, the Investigator will report adverse events to the IRB Office within the appropriate timelines documented in the institutional policies for reporting SAE and AE . .

SAE's require expedited reporting when meeting the following criteria:

- The incident is serious
- Unexpected – any adverse experience, the specificity or severity of which is not consistent with the underlying disease of the patient or with the risk described in the protocol
- At least possibly related to the study agent or other protocol specific activity

Recording of Adverse Events

Adverse event recording will begin after administration of study medication.

Diagnostic and therapeutic non-invasive and invasive (i.e. surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event, unless it is pre-existing (prior to initiating Omegaven®).

Medical conditions/diseases present before starting drug are only considered adverse events if they worsen after starting treatment.

Symptoms of the original or targeted disease are not to be considered adverse events in this treatment. The following symptoms are indicative of underlying disease and will not be reported as adverse events: hyperbilirubinemia, elevated creatinine/renal failure, weight gain, encephalopathy, hypoxia / respiratory failure, ascites, hepatomegaly and right upper quadrant pain, sepsis (culture positive or negative), emesis or

increase in stool output with the advancement of feeds or bleeding due to liver failure.

Abnormal laboratory values or test results constitute adverse events if they induce clinical signs or symptoms or require therapy. They are to be recorded on the Adverse Events CRF under the signs, symptoms or diagnoses associated with them.

As far as possible, each adverse event will be assessed by the Investigator with respect to its duration (start and end dates), the severity grade (mild, moderate, severe, life-threatening, fatal), its relationship to the drug (unrelated, unlikely to be related, possibly, probably and definitely related), the action(s) taken, the outcome (i.e. resolved, resolved with sequelae, continuing), gravity (SERIOUS or NOT SERIOUS), and expected/unexpected on the basis of drug insert.

Expected drug related events are those that have been previously identified as resulting from administration of the protocol therapy, short bowel syndrome, or parenteral nutrition as outlined in the potential risks section of this protocol or the package insert. Unexpected adverse events are those that have not been previously associated with Omegaven, short bowel syndrome, liver failure, parenteral nutrition support or any standard care for subjects with short bowel syndrome.

Adverse events will be reported by diagnosis unless a diagnosis cannot be determined.

Grading (Severity) of Adverse Events

Each adverse event will be graded to describe its intensity according to the following Severity scale:

1=	Mild:	does not interfere with patient's usual function
2=	Moderate:	interferes to some extent with patient's usual function
3=	Severe:	interferes significantly with patient's usual function

4=	Life-threatening:	puts the patient at immediate risk of death
5=	Fatal:	patient died

The NCI's Common Terminology Criteria for Adverse Events Version 4.0 (Appendix A) will be used if applicable.

Relationship to Drug

For all adverse events that occur while the patient is on drug, the relationship to the drug must be assessed by the Investigator using the following scale:

1 = not related
2 = unlikely
3 = possibly related
4 = probably related
5 = definitely related

For Grade > 3 adverse reactions which are possibly (3), probably (4) or definitely (5) related to the drug, study medication should be discontinued as described above.

Please note: For safety data analysis, not related and unlikely are considered "not attributable;" possible, probable and definite are considered "attributable." Assessment of relationship to drug must be carried out by the Investigator according to the 5-point scale above.

Gravity (Seriousness) of Adverse Events

Each adverse event is to be classified by the Investigator as SERIOUS or NOT SERIOUS.

Follow-Up after Adverse Events

All adverse events will be followed until they are resolved or the patient's participation in the treatment ends (i.e., until a final report is completed for that patient).

In addition, all SAEs and those non serious events assessed by the Investigator as attributable (i.e. possibly, probably, definitely related to the drug) will continue to be followed even after the patient's participation in the treatment is over. Such events will be followed until they resolve or until the Investigator assesses them as "chronic" or "stable." Resolution of such events is to be documented in the CRF.

XIII. Statistics

We selected a study number of 25 patients (5 patients a year for 5 years) even though, statistically, a number of 19 will be satisfactory based upon power analysis. We know from our current registry that 10% of historic controls will experience resolution of cholestasis within 8 weeks while receiving Intralipid®, and we know from the data of Gura, et al (5) that approximately 50% of experimental subjects will experience resolution of cholestasis within eight weeks while receiving Omegaven®. Thus, achieving an alpha of 0.05 and a beta of 0.80, a sample size of 19 patients and 19 controls will be adequate (11). However, insofar as this is a compassionate release protocol, we will not refuse entry into the study even if we have shown statistically that Omegaven® is efficacious. We estimate that at most we will acquire five patients per year, and we anticipate that within five years, Omegaven® or SMOF (soy, MCT, olive oil and fish oil) parenteral lipids will have obtained FDA approval for clinical use.

The analysis populations will include (1) subjects receiving Omegaven® under this protocol and (2) historical controls from our internal registry who have demonstrated cholestasis while on Intralipid®. Paired t-tests will be used to report the statistical significance of differences between means. A p value of 0.05 or less will be considered significant. Wilcoxon Tests will be used to report the statistical significant differences between medians, and x_2 tests/Fisher's exact tests will be used to report proportions. A Kaplan-Meier analysis will compare changes in conjugated/direct bilirubin concentration over time between groups. Cox proportional hazard models will be used to estimate crude and adjusted hazard ratios. Analyses will be performed via SAS 9.2 (SAS Institute Inc, Cary, NC) and S-Plus 8.1.1 (Insightful, Inc, Seattle, WA).

IX. Data Management

Each subject will be given a unique identifier. Only members of the study team will be able to link this identifier to the subject. No patient identifiers will be published.

The specific data items to be captured are age (in years), gender, race, and current medications,. All data will be stored in a secure area or in a password protected electronic file.

X. Financing

Funding will be sought from private foundations and both local and national philanthropic groups. Insurance companies will also be billed for standard of care procedures. If funding cannot be obtained from any source, internal funding by Cincinnati Children's Hospital Medical Center will be reviewed on a case by case basis.

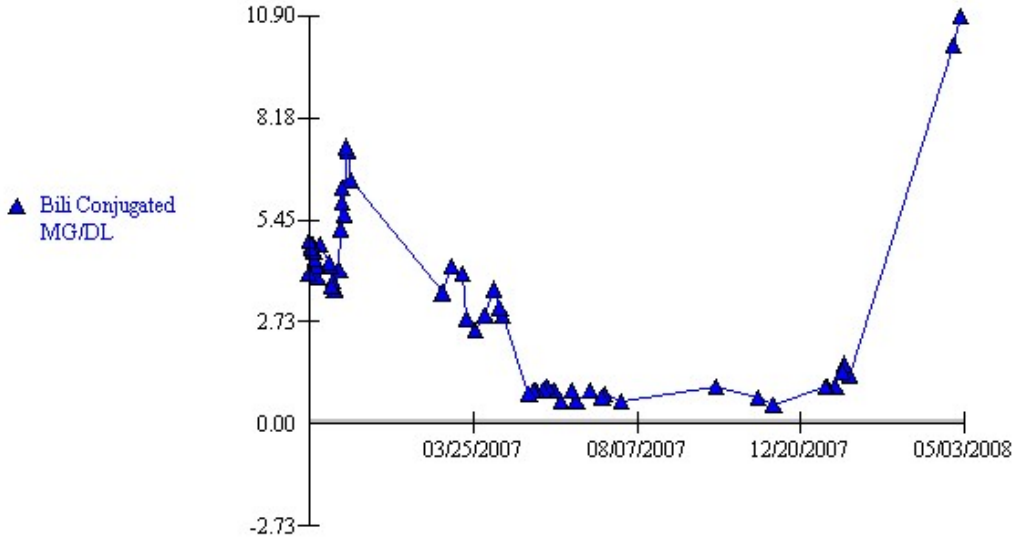

Figure 1. Conjugated bilirubin versus time in patient on Omegaven® which was started in June of 2006 when her conjugated bilirubin was approximately 6.5 mg/dl. It remained below 2 mg/dl until she developed hepatic metastases of her neuroblastoma in March of 2008.

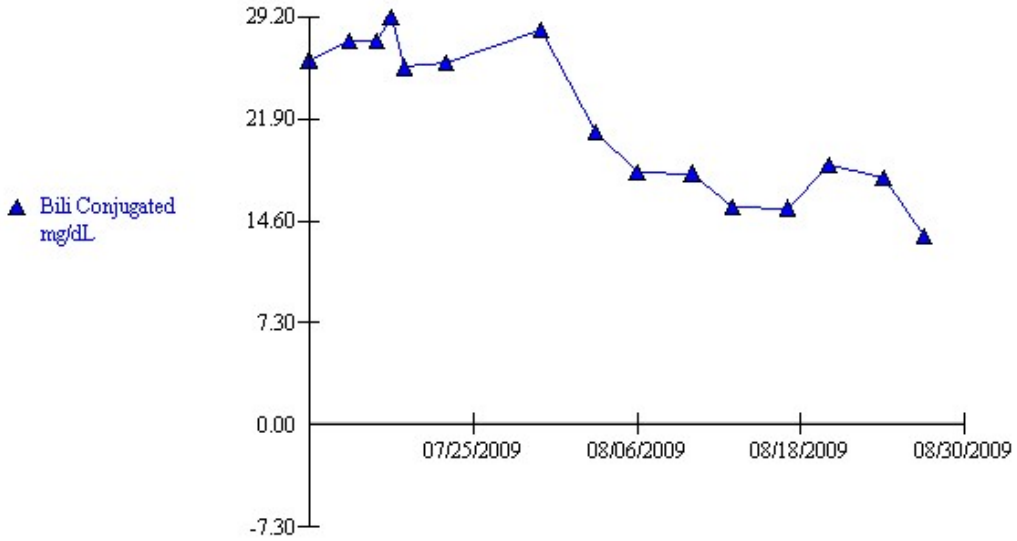

Figure 2. Conjugated bilirubin levels over time in a patient starting Omegaven® on approximately 8/1/09. Levels progressively fell while this critically ill patient was receiving minimal enteral nutrition and on TPN within the critical care unit. At the time of death, his conjugated bilirubin was less than half the level it had been when Omegaven® was started.

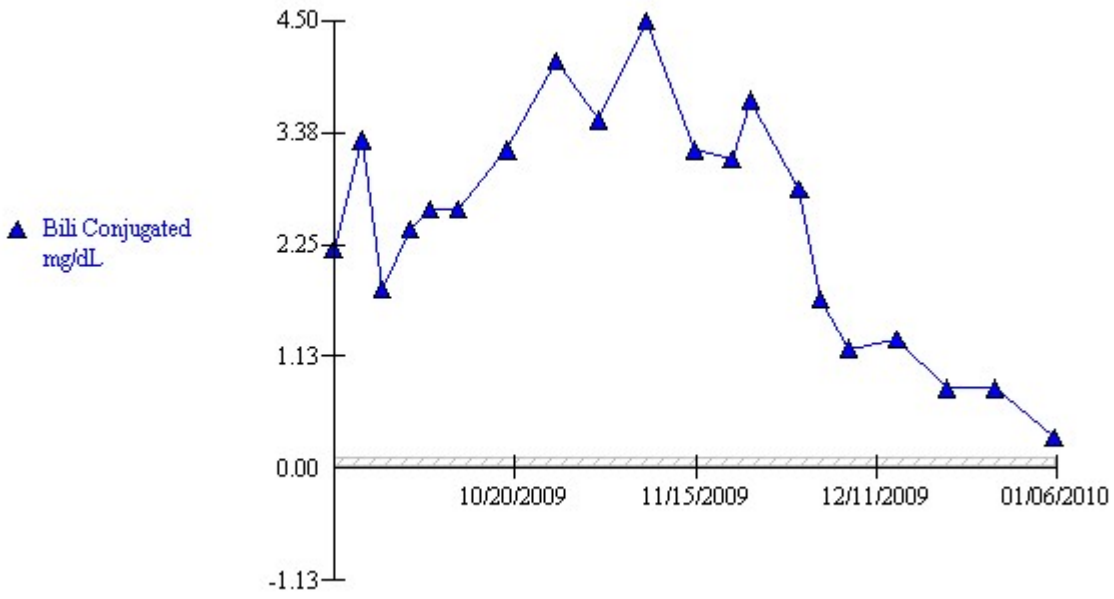

Figure 3. Conjugated bilirubin levels over time in a patient starting Omegaven® on approximately 11/15/09 when his conjugated bilirubin level was nearly at its peak. He remained on Omegaven ®, and feedings were soon begun. Within 61/2 weeks, his conjugated bilirubin had fallen below 1 mg/dl.

XI. References

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