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Compassionate Use of Omegaven in Children

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COMPASSIONATE USE PROTOCOL

Compassionate Use of Omegaven for the Treatment of Parenteral-Nutrition-Associated Liver Disease in Children (IRB 5451)

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Abstract

This is a single-group assignment, open-label protocol for the compassionate use of Omegaven® 10% in 200 children less than 6 years of age who are diagnosed with parenteral-nutrition-associated liver disease and have failed conventional lipid reduction strategies. The primary objective is to safely provide Omegaven (fish oil lipid emulsion) to Oklahoma children who are dependent on parenteral nutrition and to determine the number of these children who have resolution of their cholestasis while on the emulsion. Omegaven at the FDA maximum dose of 1 g/kg/day will be used with informed consent after the failure of conventional therapies to prevent the progression of liver disease. Children will be eligible if they are dependent on parenteral nutrition and have a direct bilirubin level of ≥2 mg/dL on two consecutive tests at least 48 hours apart while on an average of <2 g/kg/day of parenteral lipids or ≥5 mg/dL on an average of 1 g/kg/day for 7 days prior. Lab studies will be obtained to monitor safety and efficacy. Children will remain on Omegaven until their physician or guardian decides to no longer utilize the lipid emulsion. Safety outcomes and the resolution of cholestasis will be monitored and reported to the FDA and IRB.

Background and Significance

Humans cannot synthesize the precursors of ω-3 (α-linolenic acid) or ω-6 (linoleic acid) fatty acids and must obtain them from their diet. In children who cannot tolerate full enteral feeds, the standard of care is to provide parenteral nutrition including IV lipids (fats). The most commonly used IV product, introduced in 1961, is Intralipid 20%, a soybean oil-based lipid emulsion rich in omega-6 fatty acids (ω-6). Omegaven 10% (Fresenius Kabi, Germany) was introduced in Europe in 2005. Fish oil is rich in very long chain ω-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), two conditionally-essential nutrients that have low rates of conversion from their precursor, α-linolenic acid.[1,2,3]

Lipid emulsions consisting primarily of omega-6 fatty acids have been linked to the development of liver damage when used for a prolonged length of time as an excess of omega-6 has been found to be pro-inflammatory. [1,2,3] Multiple studies have shown Omegaven useful for normalizing high direct bilirubin levels in comparison with Intralipid, as omega-3 is believed to attenuate the inflammatory response.[1,2,3,4,5] Unfortunately, those receiving Omegaven as a *rescue therapy* after receiving a course of Intralipid have histologic liver specimens with decreased inflammation[6] but still demonstrate steatosis (fatty liver) and cirrhosis of the liver.[7] In a 2012 study by Puder,[8] five groups of mice received different commercially-available lipid emulsions, including Intralipid and Omegaven. The only group to complete the study with normal liver histology had received Omegaven.

A retrospective cohort study that compared ω-3 to ω-6 lipid emulsions in 39 infants showed that it took 9.4 weeks in the ω-3 group versus 44.1 weeks in the ω-6 group to reverse cholestasis. Those in the ω-3 group also had lower mortality and liver transplant rates.[9] Infants who started an ω-3 lipid emulsion with an initial direct bilirubin of <5 mg/dL had a lower mortality rate (6%) versus those who started the therapy with a direct bilirubin of >10 mg/dL (35%).[4]

One conventional therapy to prevent or treat cholestasis is lipid minimization, such that the IV lipid dose is reduced to levels below recommended intake amounts, compounding the growth failure inherent in infants with gastrointestinal disorders. In those receiving Omegaven, their dose is limited by regulations to 1 g/kg/day, also below the recommended lipid intake. Since fats have the highest caloric density of nutrients, maximizing intake is an important aspect of providing nutritional support. The combination of maximum Omegaven dosing supplemented with lower doses of Intralipid could theoretically provide a more balanced intake of essential fatty acids as well as improved growth in this vulnerable population.

Infants in our institution with severe PNALD were transferred outside of Oklahoma to centers approved to provide Omegave through "compassionate use" protocols as it is not available in the U.S. for routine use. In 2014, The Children's Hospital had approximately 130 inpatient and 30 outpatient children between birth and 18 years of age with direct bilirubin levels above 4 mg/dL.[10] Liver failure leads to approximately five liver transplants annually in Oklahoma children. While not all of these are due to parenteral nutrition, the ability to prevent even one transplant yearly would result in a massive savings of healthcare dollars as well as improved quality of life for those affected.

This protocol will help delineate the safety and efficacy of Omegaven for use in the treatment of PNALD in children less than 6 years of age. It has the potential to prevent or delay the need for liver transplantation in children who are exposed to long courses of intravenous nutrition while awaiting intestinal adaptation and growth and may provide a better alternative to our current sole use of ω-6 lipid emulsions associated with PNALD in children unable to achieve full enteral nutrition. It will also demonstrate the essential fatty acid profiles of infants receiving Intralipid (ω-6) as a sole source versus Omegaven (ω-3) as a sole source versus the combination.

PRIMARY OBJECTIVES:

To safely provide Omegaven on a compassionate use basis to Oklahoma children who are dependent on parenteral nutrition and have failed conventional lipid reduction strategies.

To determine the number of these patients who have resolution of their cholestasis (direct bilirubin < 2 mg/dL) within 60 days of initiation of the emulsion.

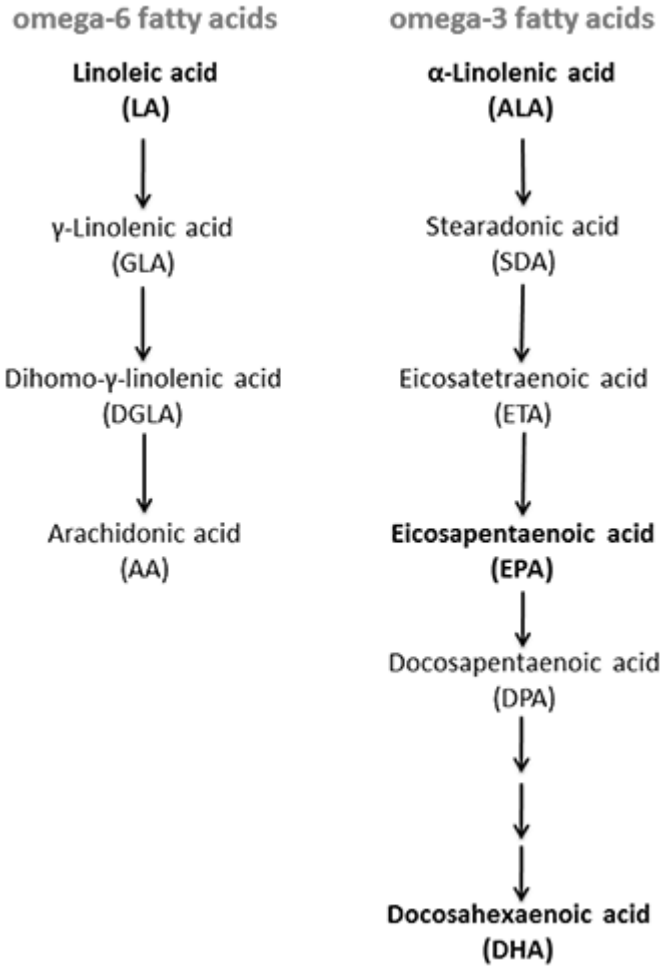
SECONDARY OBJECTIVE:

To determine if the essential fatty acid profile differs between those receiving only Intralipid, only Omegaven, or a combination.

To determine if infants who receive Omegaven have different developmental outcomes than those on Intralipid.

Lipid Emulsion Contents[8]

	Intralipid (ω-6)	Omegaven (ω-3)
Fat content (per 10 ml)	2 grams	1 gram
α-Tocopherol (vit E)	38 mg/L	150-296 mg/L
Phytosterols	348 mg/L	0 mg/L
Linoleic acid (ω-6 precursor)	50 g/L	1-7 g/L
Arachidonic acid (ω-6)	0 g/L	1-4 g/L
α-Linolenic acid (ω-3 precursor)	9 g/L	<2 g/L
Eicosapentaenoic acid (EPA; ω-3)	0 g/L	13-28 g/L
Docosahexaenoic acid (DHA; ω-3)	0 g/L	14-31 g/L



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Preliminary Studies/Progress Report

Dr. Kimberly Ernst, an associate professor at OU, has published several articles in the last 15 years specifically related to parenteral and enteral nutrition in extremely low birth weight infants. Her work is referenced in the 2009 "Nutritional Strategies for the Very Low Birthweight Infant." She provides annual nutrition training to the clinical nursing team dedicated to the treatment of extremely low birth weight infants. As the Co-Chair of the NICU Nutritional Committee, she helped develop the first standardized parenteral nutrition solution started at OUMC NICU about 10 years ago. In 2015, she helped to develop off-the-shelf parenteral solutions for improved safety, efficiency, and cost in the NICU. She is the Leader of the NICU-GI Team, an interprofessional team providing comprehensive care to children with complex gastrointestinal disorders as they transition from the inpatient setting to home.

In the summer of 2016, the FDA approved a newer generation lipid emulsion, SMOFlipid which contains a mixture of soybean oil, coconut oil (MCT), olive oil, and fish oil.[12] Many places around the country have already switched to using this blend instead of the pure soybean product, especially for children whose cholestasis has resolved and are on home parenteral nutrition. Thus, at this time, clinical practice is likely to limit Omegaven use to a maximum of 3 years unless further evidence demonstrates it is superior to SMOFlipid.

In 2017, Dr Ernst published her findings in the Journal of Perinatology that 60% of infants on lipid minimization (~1 g/kg/day) with Intralipid (n=15) were found to have essential fatty acid deficiency while none of the infants on Omegaven (n=9) did. Furthermore, those who developed essential fatty acid deficiency (n=9) had a slower weight gain (19 g/kday) than those who did not (n=15) and gained 39 g/day.[13]

Research Design and Methods

Up to 200 children will be eligible for Omegaven use if they meet the following criteria:

- Live in or temporarily relocate to Oklahoma
- Age up to 6 years, both sexes, all races
- Have received at least 14 days of parenteral nutrition
- Have a direct bilirubin level of ≥2 mg/dL for two consecutive samples at least 48 hours apart and received parenteral lipids at a maximum dose of 28 g/kg over the two weeks prior OR have a direct bilirubin level of ≥5 mg/dL and received parenteral lipids at a maximum dose of 7 g/kg over the week prior

Exclusion criteria for enrollment:

- Known food allergy to fish
- Known metabolic disorder of lipid metabolism
- Active coagulopathies (active bleeding or requiring blood product treatment in the prior 48 hours)
- Medical condition likely to result in death in the next 30 days

Baseline labs (Table 1) will be obtained within 48 hours prior to starting Omegaven. An essential fatty acid profile will demonstrate the baseline profile on Intralipid. An Omegaven infusion will be started at a dose of 1 g/kg/day after informed consent is obtained. This is the maximum dose allowed by the FDA. Monitoring studies will be obtained per Table 1. Dosing modifications will be based on the parameters found on page 7 of the protocol. After the first month of Omegaven therapy, routine study labs will be obtained as well as an essential fatty acid profile which will demonstrate the profile on Omegaven.

Once the child's direct bilirubin level has normalized (below 2 mg/dL) and they have received at least four weeks of Omegaven, additional parenteral lipids may be added or adjusted at the discretion of the physician.

Enrolled children will have full growth assessments (weight, length, FOC) and nutritional assessments at every patient encounter (typically this is daily in the hospital and at every GI clinic visit). Any surgical procedures, medications, hospital readmissions, and/or infections directly related to the use of parenteral nutrition will be documented as well as any laboratory, radiology, or pathology data obtained for this purpose while the patient is receiving Omegaven or within 30 days of stopping the lipid.

Table 1: Laboratory Monitoring

	Baseline Day 0	Weekly	Every 2 Weeks	Monthly	After Last Omegaven Dose[1]
While DB ≥2 mg/dL					
Direct bili	Day -1 to 0	±3 days			Continue weekly until normal
CBC/diff	± 3 days		±3 days		Within 7 days
AST/ALT/GGT	± 3 days		±3 days		Within 7 days
Triglycerides Lipid panel	± 3 days			±3 days	
PT/INR	± 3 days			±3 days	Within 14 days
EFAP	Day 0		±3 days		Within 30 ± 7 days
When DB <2 mg/dL					
Direct bili			±3 days		
CBC/diff			±3 days		Within 14 days
AST/ALT/GGT			±3 days		Within 14 days
Triglycerides Lipid panel				±3 days	
PT/INR				±3 days	Within 14 days
EFAP			±3 days		Within 30 ± 7 days

[1]If DB remains ≥2 mg/dL, monitoring will continue until child is off Omegaven for 4 months. When feasible, an EFAP will be obtained approximately 4 weeks after the parenteral nutrition use has ceased.

Dosing Modifications Based on Triglyceride Levels:

- If triglyceride level ≤ 250 mg/dL, continue lipids at current dose.
- If triglyceride level > 250 mg/dL, repeat specimen when off lipids for 4 hours. If repeat is ≤ 250 mg/dL, continue at current dose. If repeat is > 250 mg/dL, decrease dose by 25% and repeat within 24 hours.
- If triglyceride level >500, stop lipids immediately with repeat level within 24 hours. Restart lipids at the discretion of the physician.

Other Dosing Modifications:

- For children unable to tolerate Omegaven due to a suspected allergy or toxicity or due to active bleeding believed to be caused or worsened by the lipid emulsion, the infusion may be decreased or stopped at the discretion of the child's medical team with the reason documented.
- The attending physician may choose to decrease or stop lipids at their discretion for any reason if they determine continuing may be detrimental to the patient with

the reason documented.

- If, for any reason, the supply of Omegaven is interrupted, the infant will receive the standard of care at an equivalent dose until Omegaven is available.

Outpatient Administration:

Children receiving Omegaven at the time of discharge must be seen within the first month in the OU Children's GI Clinic as an outpatient once they are discharged from the hospital. Further outpatient visits should occur no less frequently than every 2 months while on Omegaven. Weight, length, and FOC will be obtained on all children less than 2 years of age; weight and height should be obtained on all children over the age of 2 years. At each outpatient visit, enteral and parenteral nutrition volumes should be recorded. Any surgical procedures, medications, hospital readmissions, and/or infections directly related to the use of parenteral nutrition should be documented as well as any laboratory, radiology, or pathology data obtained for this purpose. Monitoring labs will be performed as per Table 1 as long as the child remains on Omegaven.

Children will be observed in the inpatient setting for a minimum of 48 hours after the initiation of Omegaven. Children will be eligible for Omegaven administration for up to 3 years. Two months before eligibility is lost via this IND, an individual IND will be submitted by the child's physician to the FDA if they expect that the child will need to require ongoing therapy. This can be completed via a new process as of January 2017 at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/UCM490130.pdf

Option Care will be the outpatient provider for parenteral nutrition. They are familiar with the procurement and use of Omegaven and have procedures in place for providing training to the families before hospital discharge regarding the administration of parenteral nutrition as well as the reporting of potential adverse events. At the time of discharge, interested parties will be given information regarding potential AEs to be reported and how to directly contact the safety monitor and/or Dr Ernst. The family, home health nurse, primary care physician, and GI physician will report any suspected AEs to Dr Ernst and/or Susan Bedwell (safety monitor).

Data Collection:

The following data may be collected for protocol adherence and patient safety analysis.

- Name
- Medical record number
- Date of birth
- Dates of hospitalization and/or outpatient visits
- Nutritional data (enteral and parenteral)
- Growth data (weight, length/height, FOC)
- Laboratory, microbiology, and pathology data
- Medications, including Ursodiol, phenobarbital, and other enteral lipid products
- Liver and/or intestinal transplant and other pertinent surgical procedures
- Neurodevelopmental testing results
- Mortality
- Adverse event data

Termination and Completion

Termination of a patient's participation will occur if the child develops a serious adverse event definitely caused by the lipid emulsion, if the child is diagnosed after enrollment with a fish allergy or a disorder of lipid metabolism, if the child is unable to tolerate the emulsion, if the child dies, if the child's guardian decides to no longer participate, or if the attending physician feels it is in the child's best interest. In the event this occurs, the date of and reason for termination will be recorded.

Completion of the study occurs when any of the following are met: the child is no longer receiving parenteral nutrition and the direct bilirubin level is <2 mg/dL, the direct bilirubin is ≥2 mg/dL and it has been 4 months since the cessation of Omegaven, Omegaven has been used for 3 years, or the child reaches 6 years of age. This does not preclude the patient from receiving the medication, but the patient's current physician will need to apply for a treatment IND and assume monitoring of the patient.

Data and Safety Monitoring Plan

All observed or volunteered adverse events (AE) will be investigated for seriousness and causality within 48 hrs of investigator awareness. AEs will be reported from enrollment through 30 calendar days after the last administration of Omegaven. A serious adverse event (SAE) includes any untoward medical occurrence that results in death, is life-threatening, requires prolongation of existing hospitalization, or results in significant disability.

We will assess adverse events using the following scale (i.e. 3D):

0=No or mild complication
1=Moderate complication with no long-lasting effects
2=Severe, life-threatening, or disabling complication
3=Death

A=UNRELATED or UNLIKELY (clearly not related to the study or the relationship appears to be remote and other factors suggest an alternative etiology exists)
B=POSSIBLE (one or more factors suggest a possible relationship but other etiologies seem equally or more likely)
C=PROBABLE (relationship seems probable because of a clear temporal association with the interaction, lack of alternative explanations for the experience, or other factors)
D=DEFINITE (clearly related to the study procedure)

Per FDA requirements, any unexpected fatal or life-threatening suspected adverse reactions will be reported within 7 days after initial receipt of the information. Any serious, unexpected suspected adverse reactions, findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and a clinically important increase in the rate of a serious suspected adverse reaction will be reported to the FDA and all investigators within 15 days after determining that the information qualifies for reporting. Annual progress reports will be reported to the FDA within 60 days of the anniversary date that the IND becomes active (March 21, 2015). All adverse events will be reported to the IRB and the FDA on an annual basis, at minimum, when the protocol goes through annual review.

The Principal Investigator will meet with a data safety monitor, Susan Bedwell, APRN (clinical nurse specialist), quarterly to review any AE that were observed or volunteered over the previous quarter.

IRB Information

1) Sources of research material

The EMR will be utilized for obtaining clinical data, study outcomes, and

information necessary for adverse event reporting. Laboratory work will be done as part of routine care and FDA requirements for receiving the emulsion.

2) Recruitment and Consent
   a. Consent will occur either in the hospital setting at the patient's bedside or in the outpatient clinic in a private room.
   b. The consent and HIPAA forms will be printed in English and Spanish. Spanish-speaking families will be consented using a Spanish-speaking interpreter provided by the hospital. Families speaking languages will be informed via a language-specific translator and will be asked to sign the English consent form.
   c. Parents/guardians will be provided the study forms, including the consent, with ample time to review the materials.
   d. Families who would like to participate will need to be transferred to The Children's Hospital at OUMC where the formal consent process will occur. The study is listed on ClinicalTrials.gov where the public has access to information regarding the study. It is possible that hospital social media or television advertisement may include information about this study.

3) Intravenous nutritional products carry the risk associated with parenteral administration, including line sepsis and extravasation. In previous published studies, there have been no additional identified risks of adverse events associated with the administration of fish oil-based lipid over soybean oil-based lipid.

4) Data will be collected by the study personnel in a private and confidential manner using the password-protected EMR or on paper forms in the patient's chart. Any data collected for analysis will be kept in a password-protected database (REDCap) or Excel file on a secure server or in the locked offices of the investigators.

5) Children may have direct benefit from participating in this study because they have access to a nutritional treatment that is suggested to be beneficial in the treatment of PNALD without a higher risk of adverse effects than the standard treatment. There may also be decreased sepsis and other adverse outcomes associated with inflammatory processes as well as the possibility of enhanced visual and neurodevelopmental outcomes with the inclusion of DHA in Omegaven.

6) Despite not being FDA-approved, Omegaven has been in use in the US for the last decade for "compassionate use" and is approved for use in other countries in Europe. Potential benefits include the possibility of preventing progressive liver damage associated with long-term ω-6-fatty acid lipid emulsions.

7) Several studies have shown the efficacy of Omegaven in resolving cholestasis

without any serious side effects reported. Children in this study may benefit from receiving a medication that provides protection against developing liver damage that is associated with the current standard treatment. The patient's insurance will be billed for the lipid emulsion at reasonable cost of acquisition plus storage and dispensing costs and the hospital has agreed to pursue payment as they do for all other treatments, including the use of charity, etc.

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