Treatment Use of Omegaven for treatment with Parenteral Nutrition Associated Liver Disease

Principal Investigator:
Joel Lim, MD, principal investigator, CMH, Gastroenterology, 234-3017, jdlim@cmh.edu

Co-Investigators:
Tracy Sandritter, PharmD, sub-investigator, CMH, Pediatric Pharmacology and Medical Toxicology, 234-9301, tlsandritter@cmh.edu

Kim Radford, RN, MSN, CPNP-AC, sub-investigator, CMH, Gastroenterology, 983-6748, kradford@cmh.edu

William San Pablo, MD, sub-investigator, CMH, Gastroenterology, 983-6658, wsanpablo@cmh.edu

Walter Andrews, MD, sub-investigator, CMH, Transplant Surgery, 234-3633, wandrews@cmh.edu

Rich Hendrickson, MD, sub-investigator, CMH, Transplant Surgery, 983-6335, rjhendrickson@cmh.edu

Beth Lyman, RN, CNSN, sub-investigator, CMH, Gastroenterology, 855-1766, blyman@cmh.edu

Research Personnel:
Corey Schurman, MA, coordinator, CMH, Gastroenterology, 802-1167, crschurman@cmh.edu

Shawna Ricks, RN, MSN, CCRC, coordinator, CMH, Gastroenterology, 234-3197, sricks@cmh.edu

Study Site(s): Children's Mercy Hospital

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1. STUDY OBJECTIVES/HYPOTHESIS

Primary Objective

To evaluate whether established parenteral nutrition associated liver disease (PNALD) can be reversed or its progression halted by using a parenteral fat emulsion prepared from fish oil (omega-3 fatty acid emulsion, Omegaven®) as measured by normalization or decrease of serum levels of hepatic enzymes.

Secondary Objective

To assess the safety profile of the intravenous omega-3 fatty acid emulsion (Omegaven®).

2. BACKGROUND

Patients suffering from short bowel syndrome require life-saving parenteral nutrition (PN). One of the major complications of this essential therapy is PNALD, especially in infants and children. This liver injury affects the majority of infants and children on long term PN and may progress to liver failure, liver transplantation or ultimately death. A number of causes of PNALD have been proposed, including the use of intravenous fat emulsions.

PN provides intravenous nutritional supplementation for patients unable to absorb adequate enteral nutrients secondary to insufficient intestinal length or decreased functionality. PN contains the macronutrient building blocks of the human diet in their most elemental forms (amino acids and dextrose) and is commonly administered with a lipid emulsion to avoid essential fatty acid deficiency and to provide a calorically dense source of non-protein calories. In addition, PN contains the essential micronutrients (electrolytes, trace elements, and vitamins) to provide an optimal nutritional regimen. Before the development of PN, patients with insufficient gastrointestinal absorptive function commonly died of starvation and subsequent complications of malnutrition. Today many patients (30,000) patients are permanently dependent on PN for survival. However, PN continues to be associated with hepatic injury that occurs at an unpredictable rate and includes both biochemical (elevated serum aminotransferases and alkaline phosphatase) and histological alterations such as steatosis, steatohepatitis, lipidosis, cholestatis, fibrosis, and cirrhosis.

Parenteral lipid emulsions in the United States are soy-based products which are rich in omega-6 fatty acids. These emulsions have been implicated in predisposing patients to PNALD because of their phytosterol content, which is thought to have a deleterious effect on hepatic biliary secretion and cause accumulation of lipids in the liver. On the other hand, animal studies have shown that intravenous fat emulsions prepared from fish oil, which are high in omega-3 fatty acids, do not impair bile flow and may actually diminish fat accumulation in hepatocytes. Fish oil based emulsions (ie, Omegaven) are available in Europe. Due to regulatory and manufacturing limitations, these products are not available to patients in the US unless their physician petitions the Food and Drug Administration for permission to import them on a compassionate use basis.

Children's Hospital, Boston has published data regarding the use of Omegaven in patients with PNALD.

It has been their experience, that through the use of Omegaven instead of conventional lipid emulsions, that the biochemical tests of liver function improved significantly.

There has been no documented case of heavy metal contamination with the use of Omegaven. There is no discussion in the literature of there being any worry or risk of this happening.

3. DESIGN

This is a compassionate use protocol for patients with PNALD who have failed traditional treatment to receive Omegaven through an IND.

TARGET POPLUATION SPECIFICS

We will be enrolling up to 10 patients 0- less than18 years of age who have Parenteral Nutrition Associated Liver Disease. These patients will have been on traditional TPN for on average 2-4

weeks and will remain on TPN using Omegaven until they no longer need TPN or are sent for short bowel or liver transplant.

Inclusion Criteria

1. The patient will be PN dependent and unable to meet nutritional needs solely by enteral nutrition.
2. Patient will be <18 years of age.
3. Direct bilirubin > 2.0mg/dl
4. The patient must have failed standard therapies to prevent progression his/her liver disease.

Exclusion Criteria

1. Other causes of chronic liver disease (Hepatitis C, Cystic fibrosis, biliary atresia, and alpha 1 anti-trypsin deficiency).
2. Patients who are allergic to eggs/shellfish
3. Patients who have severe hemorrhagic disorders.

5. DATA COLLECTION

Data Collection Procedures

Patients will be identified by Dr. Lim and the Intestinal Rehabilitation/Transplant Team.

All potential patients will be either inpatient admitted under the GI or Surgery Service, or GI or Surgery Services will be consulted. Dr. Lim or one of the sub-investigators will be notified by the services (if he is not the attending) that a subject has clinically progressed towards needing the investigational drug. Dr. Lim will ultimately decide if a subject meets criteria for enrollment.

When Dr. Lim feels a patient will benefit from Omegaven, he or one of the sub-investigators will discuss the protocol with the family and answer all questions. Permission/assent will be obtained by the PI, sub-investigators or coordinator.

Records to be kept

All data collection will be part of the patient's medical record and there is no plan to record any additional data. A patient record will be kept with lab results and other information directly related to a subject's response to Omegaven. This record will be identified with a unique study number and a master linking list will be maintained that links the subject's medical record number to their study number.

Secure Storage of Data

The patient record will consist of an excel spread sheet that will be located in the GI section folder on the CMH network. The linking list will be kept in a separate folder in the GI section folder. Only the PI and coordinators will have access to these folders.

STUDY DURATION/STUDY TIMELINE

This protocol will be kept open indefinitely for the benefit of patients who have PNALD and need access to Omegaven through this IND.

STATISTICAL CONSIDERATIONS

As this is a compassionate use protocol, there are no real statistical considerations. All subjects who could benefit from Omegaven will be included.

Institutional Review Board (IRB) Review and Informed Consent

This protocol, and any subsequent modifications, will be reviewed and approved by the Pediatric IRB at The Children's Mercy Hospital & Clinics.

Permission/assent will be obtained after Dr. Lim has decided that a patient would benefit from Omegaven therapy and all other standard therapies have been exhausted. Permission/assent will be obtained in person and as the subjects will all be inpatients, will most likely be obtained in the NICU or PICU. Without this treatment, the next step for these patients is short bowel or liver transplant.

Subject Confidentiality

All data collection will be part of the patient's medical record and there is no plan to record any additional data. A research record will be kept with lab results and other information directly related to a subject's response to Omegaven. This research record will be identified with a unique study number and a master linking list will be maintained that links the subject's medical record number to their study number.

All research records will be kept on an excel spreadsheet in a protected folder which only the PI and coordinators will have access to. There are no patient identifiers recorded in the research record. All computer entry and networking programs will be done using study identification only. All data will be entered into a computer that is password protected. All data will be maintained for a minimum of three years after completion of the protocol.

Study Modification/Discontinuation

The protocol may be modified or discontinued at any time by the IRB, the OHRP, the FDA or other Government agencies as part of their duties to ensure that patients are protected.

PUBLICATION OF RESEARCH FINDINGS

There are no plans to publish findings, however, there is always the chance that something may be found during the course of treatment that would be of scientific merit and would be of benefit to add to the literature on Omegaven.