Hepatic Explant Pathology of Pediatric Intestinal Transplant Recipients Previously Treated with Omega-3 Fatty Acid Lipid Emulsion

Cal S. Matsumoto, MD[1], Stuart S. Kaufman, MD[1], Eddie R. Island, MD[1], Bhaskar Kallakury, MD[2], Nada A. Yazigi, MD[1], Khalid M. Khan, MD[1], and Thomas M. Fishbein, MD[1]

Objective To evaluate and compare the biochemical and histologic effect of parenteral fish oil lipid emulsion that is rich in omega-3 polyunsaturated fatty acids (O3FAs), Omegaven (Fresenius Kabi AG, Bad Homburg, Germany) with standard omega-6 polyunsaturated fatty acid (O6FA) parenteral nutrition.

Study design Comparison of hepatic explant pathology and biochemical outcome on pediatric patients with intestinal failure treated with either parental O3FA or O6FA who had received a liver-inclusive intestine transplant.

Results Seven liver-inclusive intestinal transplants were performed in 7 patients who received O3FA for a mean of 62% ± 13% of total patient life-span (16.1 ± 7.0 months) before transplant. Median total bilirubin fell from 6.9 mg/dL at the start of treatment to 0.7 mg/dL at the time transplant ($P < .02$), which was a significant decrease compared with the similarly matched O6FA cohort ($P = .012$). All 7 of the 03FA-treated patients received a liver-inclusive intestinal transplant had advanced fibrosis (stage 3 or 4) noted on explant pathologic examination, despite a resolution of cholestasis at the time of transplant. Histologic inflammatory scores were lower ($P = .056$) in the 03FA group with similar degrees of advanced fibrosis as in the O6FA group.

Conclusions In a matched comparison of patients undergoing intestinal transplantation with a history of extended O3FA lipid emulsion therapy that successfully reversed hyperbilirubinemia, significant hepatic fibrosis was present in the explanted livers despite a reduction in inflammation. This result confirms concern that the use of O3FA may have a limited role in altering the development of hepatic fibrosis from parenteral nutrition. *(J Pediatr 2014;165:59-64)*.

Liver disease occurs in as many as 60% of infants with intestinal failure, defined as long-term dependence on parenteral nutrition for survival in the setting of an anatomically short or functionally defective gastrointestinal tract.[1] Parenteral nutrition-associated liver disease (PNALD) can lead to chronic liver failure, historical incidence of which may be as high as 25%-40%.[2-5] A combination of factors is thought to be responsible for PNALD; chief among these are pro-oxidant nutritional stressors, including omega-6 fatty acid (O6FA)-rich, soy oil-based intravenous lipid emulsion. An inflammatory host milieu resulting from abdominal sepsis and perpetuated by central line-associated blood stream infection and the state of massive small bowel loss itself are thought to contribute.[1,2]

Impending liver failure because of PNALD and other life-threatening complications of parenteral nutrition including critical loss of central vein access and recurrent sepsis and severe fluid/electrolyte disturbances are appropriate indications for intestinal transplantation.[6,7] Reflecting the historically high incidence of rapidly progressive PNALD in small children, a majority of those receiving an intestinal transplant have also required a simultaneous liver transplant. Consequently, innovations that improve tolerance of parenteral nutrition in intestinal failure may reduce the need for rescue transplantation.

Reports have suggested that substitution of O6FA with a product based on fish oil that is rich in omega-3 polyunsaturated fatty acids (O3FAs), Omegaven (Fresenius Kabi AG, Bad Homburg, Germany), ameliorates hyperbilirubinemia in children and adults with intestinal failure.[8-15] Even though early hepatic decompensation appears to be aborted by resolution of hyperbilirubinemia, a long-term benefit from O3FA lipid emulsion is unclear; reports suggest that liver fibrosis may persist, and perhaps progress.[16-18] As treated patients come to transplantation, either because of PNALD resistant to O3FA therapy or because of other complications of long-term parenteral nutrition, we have been afforded a unique opportunity to assess the impact of O3FA lipid emulsion on liver histopathology and function. We hypothesized that analysis of end-stage liver explants of patients treated with O3FA might suggest possible mechanisms for apparent O3FA failure in comparison with untreated patients. This may guide future research into optimal uses of this product. In pursuit of this hypothesis, we compared livers that were replaced with intestine after extended O3FA treatment to those from a matched cohort of

ALT	Alanine aminotransferase
ECM	Extracellular matrix
O3FA	Omega-3 fatty acid
O6FA	Omega-6 fatty acid
PNALD	Parenteral nutrition-associated liver disease

From the [1]MedStar Georgetown Transplant Institute, Georgetown University Hospital; and [2]Department of Pathology, MedStar Georgetown University Hospital, Washington, DC

The authors declare no conflicts of interest.

0022-3476/$ - see front matter. Copyright © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jpeds.2014.03.034

patients contemporaneously undergoing combined liver-intestinal transplant who previously received exclusively O6FA lipid emulsions.

Methods

Charts were reviewed of all pediatric (age <18 years) patients listed or referred for intestinal transplantation between November 2003 and June 2012 who were treated with O3FA for at least 30 days prior to transplantation. All patients enrolled in this study were originally referred for consideration of intestinal transplantation because of refractory intestinal failure with the expectation of poor survival on parenteral nutrition. In all cases, O3FA was maintained continuously at a dose of 1 g/kg infused over 12 hours daily with simultaneous cessation of O6FA until transplant.[8] Standard laboratory testing for intestinal failure management included weekly serum measurements of serum aspartate aminotransferase, alanine aminotransferase (ALT), alkaline phosphatase, total and direct bilirubin, serum albumin, and platelet count.[4] The rationale for listing individual patients for transplantation were as per current guidelines.[6,7] Specifically, declining central vein access was defined as occlusion of at least one-half of standard central vein access sites when permanent parenteral nutrition was anticipated, and recurrent central line associated bloodstream infection was defined as the development of 2 or more episodes of systemic sepsis per year. The decision to include a liver allograft in the transplant was based on clinical features of advanced liver disease, especially features of portal hypertension, including hepatomegaly and functional hypersplenism, irrespective of the presence or absence of hyperbilirubinemia.[2] Percutaneous liver biopsy was performed in ambiguous cases. Consideration of donor organs offered for implantation and technical aspects of isolated intestine, liver-intestine-pancreas, and multivisceral transplantation were as described previously.[19,20]

A cohort of matched pediatric liver-inclusive intestinal transplant recipients who received O6FA at a dose of 1-3 g/kg/d as a standard component of parenteral nutrition initiated in the neonatal period and who underwent transplantation contemporaneously with the O3FA-treated patients served as the comparison group. This study was reviewed and approved by the Institutional Review Board of Georgetown University.

All liver transplant explants and biopsy specimens were examined by MedStar Georgetown University Hospital Department of Pathology attending staff blinded to the type of lipid utilized in individual patients using standard staining methods including hematoxylin and eosin and Masson trichrome. Hepatic inflammation and fibrosis of liver tissue were evaluated and graded according to the Batts and Ludwig system.[21]

Statistical Analyses

Continuous variables from various patient groups were compared with the Student t test and 1-way ANOVA for normally distributed data and the Mann-Whitney and Kruskal-Wallis tests for non-normally distributed data, central tendencies of which were expressed as means plus or minus SD or medians with ranges as noted, respectively. Correlations were tested using Kendall tau test, and Fisher exact test (Freeman-Halton extension for 2×3 contingency table) was also used for group comparison where indicated. Statistical analyses were performed using StatsDirect (Cheshire, United Kingdom) and Analyse-it (Leeds, United Kingdom) software. Significance was taken as $P < .05$.

Results

Between November 2003 to June 2012, 154 intestinal transplants (74 adult/80 pediatric) were performed in 149 patients. Of the 80 pediatric intestinal transplants, 9 transplants were performed in 9 patients who received O3FA for at least 30 days by 6 referring centers and our program in the pretransplant period, all between November 2008 and May 2012. In all cases, O3FA was initiated because of sustained hyperbilirubinemia in the setting of expected need for prolonged parenteral nutrition when third party providers would pay for this investigational new drug (in the US). Of these 9 patients, 7 received a liver-inclusive intestinal graft, and 2 received an isolated intestinal graft.

O3FA before Liver-Inclusive Transplant

Demographic information on these 7 patients is summarized in Table I. Mean gestational age of the cohort was 32.8 ± 5.9 weeks. Necrotizing enterocolitis was the most common cause of intestinal failure, occurring in 2 of the 7, whereas only 1 patient had a functional diagnosis (total intestinal Hirschsprung disease). For the 6 patients with short gut syndrome, mean remnant small bowel (jejuno-ileal) length at transplant was 5.7 ± 2.7 cm. Median age and body weight at transplant equaled 21.1 months and 12.7 kg, respectively.

Data pertaining to administration of O3FA and the hepatic response in each of the 7 patients receiving a liver-inclusive transplant are listed in Table II. In summary, median age at initiation of O3FA was 9.3 months, and mean duration of treatment equaled 16.1 ± 7.0 months, which was equivalent to 61.8% ± 13.4% of total patient life-span before transplant. Younger age at initiation of O3FA was associated with a greater percentage of total life on therapy ($\tau = -0.781$, $P = .0075$). Median total bilirubin fell from 6.9 mg/dL at the start of treatment to 1.7 mg/dL after 3 months ($P < .01$), and further decreased to 0.7 mg/dL at transplant ($P < .02$). In contrast with the decline in serum bilirubin under O3FA therapy, there were no significant improvements in laboratory markers of hepatocellular inflammation (median ALT pre-therapy 146 U/L vs ALT post-therapy 169 U/L), hepatocellular synthetic function (median albumin level pre-therapy 3.1 g/dL vs albumin post-therapy 3.2 g/dL), or portal hypertension (mean platelet count pre-therapy $160 \pm 62 \times 10^3/\mu L$ vs platelet count post-therapy $120 \pm 50 \times 10^3/\mu L$).

Download English Version:

https://daneshyari.com/en/article/4164867

Download Persian Version:

https://daneshyari.com/article/4164867

Daneshyari.com