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Changing the Paradigm: Omegaven for the Treatment of Liver Failure in Pediatric Short Bowel Syndrome

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ABSTRACT

Background: Parenteral omega-3 fatty acids, such as Omegaven, may benefit patients with pediatric short bowel syndrome (SBS) who develop parenteral nutrition–associated liver disease (PNALD).

Patients and Methods: Retrospective cohort describing the outcome of all 12 children with SBS and advanced PNALD who were treated with Omegaven (target omega-6 to omega-3 fatty acid ratio = 1:1 to 2:1).

Results: The median age was 7.5 (range 3.6–46) months, and median parenteral nutrition duration before starting Omegaven was 28.4 (range 15.3–55.3) weeks. Median initial serum conjugated bilirubin was 137 (range 54–203) μmol/L (8.06 [3.18–11.94] mg/dL). Of the 12 patients, 9 had complete and sustained resolution of hyperbilirubinemia within a median of 24 (range 7–37) weeks, and all are no longer being considered for liver transplantation. Improvements in markers of hepatic inflammation as well as nutritional status also were noted in these patients. Three patients received a liver-intestine transplant while taking Omegaven. There were no complications attributable to Omegaven.

Conclusions: Omegaven is associated with restoration of liver function in patients with SBS and advanced liver disease. Parenteral omega-3 fatty acids, such as Omegaven, have the potential to fundamentally alter the paradigm of neonatal SBS from one of early death or transplantation from liver failure to a more chronic disease. More children with SBS should achieve full enteral tolerance and those who do not have the capacity for intestinal adaptation should be able to survive and receive an intestinal graft when older. ***JPGN 48:209–215, 2009.*** **Key Words:** cholestasis—omega-3 fatty acids—parenteral nutrition—short bowel syndrome. © 2009 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Pediatric short bowel syndrome (SBS) is a devastating condition, occurring in 24.5/100,000 live births (1). Case fatality estimates have been cited as high as 50%, and the disorder has been demonstrated to account for 1.4% of deaths in children younger than 4 years of age (1). The mortality and morbidity of pediatric SBS is primarily related to the development of end-stage parenteral nutrition–associated liver disease (PNALD).

Overall, PNALD is the most common complication in children with SBS, occurring in 67% of patients (2). Although cessation of parenteral nutrition (PN) will result in resolution of PNALD (3), up to 25% of children with SBS progress to irreversible liver failure (4). Once liver failure becomes established, the only treatment option to date has been liver and/or intestinal transplantation. This poses a significant challenge in this patient population, due to a severe shortage of size-appropriate grafts. As a result, many of these children have died while awaiting an allograft (5). Furthermore, the long-term outcome of liver-intestinal transplantation remains poor, with a 5-year graft survival of only 50% (6). For these reasons, prevention and treatment of PNALD have been viewed as critical yet elusive goals in the management of infants with SBS.

Recent evidence from animal models as well as data from a single center (Boston Children's Hospital) have suggested that replacement of the typical soy-based predominantly omega-6 fatty acid (ω6FA) PN lipid emulsion Intralipid (Fresenius Kabi, Bad Hamburg, Germany) with a fish oil–based lipid emulsion containing omega-3 fatty acids (ω3FA) has the potential to reverse liver disease in infants with SBS (7,8).

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The objective of this report is to describe our early experience and results with Omegaven (Fresenius Kabi), a predominantly ω3FA lipid emulsion, in the management of children with SBS and advanced PNALD.

PATIENTS AND METHODS

Since April 2006, we have treated all children with SBS and severe PNALD with Omegaven. Our criterion for initiating Omegaven was severe PNALD as defined by a serum-conjugated bilirubin greater than 100 μmol/L (5.9 mg/dL) or a serum-conjugated bilirubin greater than 50 μmol/L (2.9 mg/dL) with other evidence of liver dysfunction, such as radiological evidence of portal hypertension, or clinical evidence of malnutrition or recurrent sepsis. Individual approval for each child treated with Omegaven was obtained under the Special Access Program of the Health Products and Food Branch of Health Canada. The Special Access Program is a program that provides approval for use of medications that have not yet received regulatory approval in Canada for use on a case by case basis. The program does not provide funding for the medication, which in the case of Omegaven was provided by our publically funded hospital.

All children with SBS at our institution are studied by a multidisciplinary intestinal rehabilitation team, the Group for Improvement of Intestinal Function and Treatment (GIFT), as has been described previously (4). Furthermore, we use a consistent definition, adopted by the Canadian Association of Pediatric Surgeons, for the diagnosis of SBS, namely children who following bowel resection remain taking PN 42 days postresection or have an intestinal length of less than the 25th percentile for gestational age (4). Before being considered for Omegaven therapy, all of the patients underwent assessment by a pediatric hepatologist to rule out other etiologies of liver disease.

Administration of Omegaven

Once approval for Omegaven is obtained, the child's PN prescription is modified such that they receive 1.5 g/kg of Intralipid and 0.5 g/kg of Omegaven for 1 week to ensure tolerance of Omegaven. Following this, they receive 1 g/kg of Intralipid and 1 g/kg of Omegaven. All of the patients taking Omegaven were studied and reviewed regularly by the multidisciplinary team. Weekly PN blood work (complete blood count, electrolytes, direct bilirubin, liver enzymes, triglycerides, and coagulation parameters) is done on all of the patients while hospitalized and then monthly for those who are on home PN. Enteral feeding is actively promoted, and typically inpatients are reviewed weekly at our multidisciplinary meeting of the GIFT team and at monthly clinics for outpatients (4). The optimal dosing strategy remains to be determined; therefore, if team consensus was that a PNALD case showed failure to improve or worsened despite Omegaven therapy (based on the pattern of direct bilirubin and liver enzymes), the Intralipid was reduced or discontinued.

Study Methodology

This article presents a retrospective cohort of all patients who have been treated with Omegaven at our institution, a quaternary pediatric referral center, from April 1, 2006, until November 9, 2007. Data were abstracted by chart review by a single reviewer. Starting 1 week before initiation of Omegaven, data collected included serum direct bilirubin, markers of hepatic inflammation (ALT, AST, and γ-glutamyl transferase), serum albumin, international normalized ratio, and the PN lipid composition, the ratio of enteral to parenteral calories, and any intercurrent significant clinical events. The primary data points for analysis were the values obtained at the initiation of Omegaven, resolution of hyperbilirubinemia, and the end of follow-up. When appropriate, paired *t* tests were performed to examine the change in a marker between time points using SPSS (version 14). Approval for this review was obtained from our institutional research ethics board (no. 1000010784).

RESULTS

Twelve children have been treated with Omegaven. Demographic data are presented in Table 1. Median age at initiation of Omegaven was 7.5 months (range 3.6–46 months), and the median duration of PN before initiation of Omegaven was 28.4 weeks (range 15.3–55.3 weeks). All but 1 of the children received a diagnosis of anatomic SBS, with the remaining patient having intestinal failure

TABLE 1. *Demographic data*

Case	Diagnosis	Sex	Gestational age at birth, wk	Age at Omegaven initiation, mo	Duration of PN before Omegaven, wk
1	Gastroschisis	F	34	12.8	55.3
2	Volvulus	F	33	9.3	40.3
3	Jejunal atresia	M	37	7.8	33.4
4	Jejunal atresia	M	35	46.0	20.9
5	Gastroschisis	F	35	5.9	25.3
6	MVID	M	40	9.8	38.7
7	Gastroschisis	M	37	7.1	30.7
8	Jejunal atresia	F	36	3.6	15.3
9	Volvulus	M	37	4.1	17.3
10	NEC	M	30	6.6	26.0
11	NEC	F	31	10.0	42.3
12	NEC	M	33	5.5	23.0

PN = parenteral nutrition; MVID = microvillus inclusion disease; NEC = necrotizing enterocolitis.

TABLE 2. *Treatment outcome*

Case	Starting direct bilirubin, μmol/L	Starting EN tolerance, %	Dose of Intralipid before treatment, $g \cdot kg^{-1} \cdot day^{-1}$	Details of lipid therapy beyond initial run-in week until resolution of hyperbilirubinemia or transplant*	Time to direct bilirubin 0 μmol/L, wk	EN tolerance when direct bilirubin 0 μmol/L, %	Total follow-up, wk	Direct bilirubin at last follow-up, μmol/L	EN tolerance at last follow-up, %
1	203	58	1.4	1 IL + 1 OM × 25 wk	26	0	81	0	25
2	84	84	1	1 OM × 11 wk Peak bilirubin before sole OM = 75 μmol/L	12	95	63	0	100
3	146	65	2.3	1 IL + 1 OM × 9 wk then 1 OM × 2 wk Peak bilirubin before sole OM = 189 μmol/L	–	–	12	222†	70
4	191	34	0.9	1 IL + 1 OM × 10 wk	11	58	62	0	90
5	138	0	2.7	1 IL + 1 OM × 8 wk then 1 OM × 16 wk Peak bilirubin before sole OM = 159 μmol/L	27	0	61	0	0
6	136	0	1.4	1 IL + 1 OM × 23 wk	24	0	55	0	0
7	54	67	2	1 IL + 1 OM × 7 wk	7	70	33	0	100
8	105	0	3	1 IL + 1 OM × 19 wk then 1 OM × 28 wk Peak bilirubin before sole OM = 108 μmol/L	–	–	48	299†	0
9	143	14	2.8	1 IL + 1 OM × 3 wk then 1 OM × 18 wk Peak bilirubin before sole OM = 158 μmol/L	22	86	37	0	100
10	68	0	1.5	1 IL + 1 OM × 16 wk then 1 OM × 15 wk Peak bilirubin before sole OM = 85 μmol/L	–	–	32	56†	0
11	117	30	1.1	1 IL + 1 OM × 9 wk then 1 OM × 27 wk Peak bilirubin before sole OM = 140 μmol/L	37	40	37	0	40
12	226	0	2.9	1 OM × 25 wk Peak bilirubin before sole OM = 322 μmol/L	26	78	26	0	78

EN = enteral; IL = intralipid; OM = Omegaven.

* Dose in $g \cdot kg^{-1} \cdot day^{-1}$ by number of weeks.

† Patient transplanted; bilirubin represents level immediately before transplant.

from a mucosal enteropathy (microvillus inclusion disease). At the time that Omegaven was initiated, all had either been listed for liver and or intestinal transplantation or were undergoing assessment by our transplant program. One patient (case 1) previously had undergone an isolated liver transplant (9) and had developed recurrent PNALD in her grafted liver.

Table 2 presents nutritional and conjugated bilirubin data for all patients treated. The median starting serum conjugated bilirubin was 137 μmol/L (range 54–226 μmol/L; 8.06 [3.18–11.94] mg/dL). Of the 12 subjects, 9 have had complete resolution of hyperbilirubinemia (serum conjugated bilirubin = 0 μmol/L); 3 patients received liver-intestine allografts while being treated with Omegaven. There have been no complications or derangements in coagulation parameters that have been attributed to Omegaven.

The 9 children who demonstrated complete resolution of hyperbilirubinemia achieved this within a median of 24 weeks (range 7–37 weeks). The median starting serum conjugated bilirubin was 138 μmol/L (range 54–226 μmol/L; 8.12 [3.18–11.94] mg/dL). Four achieved complete resolution of hyperbilirubinemia while receiving parenteral lipids containing both Intralipid and Omegaven, whereas in 5 resolution of hyperbilirubinemia occurred after discontinuation of the Intralipid. Median gain in enteral tolerance from the time that Omegaven was initiated to resolution of hyperbilirubinemia was negligible at 10% (range −58% to 78%). However, those with an enteral tolerance greater than 30% at the time of initiation of Omegaven demonstrated faster resolution of PNALD (14.0 vs 27.2 weeks; $P = 0.026$). In addition to resolution of hyperbilirubinemia, there was also evidence of reduction in hepatic inflammation (serum transaminases) and a statistically significant increase in serum albumin during this time period (Table 3). With median follow-up of 31 weeks (range 0–55 weeks) since resolution of hyperbilirubinemia, all of the patients remain well, without any clinical evidence of PNALD. All of them have been delisted for liver transplantation or have had their transplant assessment terminated. At last follow-up, 6 remain on parenteral nutrition (median PN support 67.5%; range 10%–100%) and continue taking Omegaven. PN has been stopped in 3 with achievement of full enteral tolerance.

Three of the patients received a liver-intestine transplant while taking Omegaven. One of these subjects (case 3) had an increase in bilirubin from 146 to 222 μmol/L (8.59–13.06 mg/dL) in the 14 weeks taking Omegaven before his transplant. He had demonstrated an initial decline in serum bilirubin, but his course was complicated by 2 septic episodes with subsequent progression of hyperbilirubinemia. The second patient (case 8) demonstrated an initial sluggish response with a decline in serum bilirubin from 105 to 62 μmol/L (6.18–3.65 mg/dL) during the first 32 weeks of treatment. However, since an episode of fungal sepsis at that time, she has shown progressive liver disease and received a transplant 48 weeks after starting Omegaven. Serum bilirubin at the time of transplant was 299 μmol/L (17.59 mg/dL). The third patient (case 10) demonstrated stable liver disease during 32 weeks of Omegaven treatment (starting serum conjugated bilirubin = 68 μmol/L [4 mg/dL]; bilirubin at transplant = 56 μmol/L [3.29 mg/dL]), but received a transplant because he had no meaningful chance of intestinal rehabilitation as a result of ultrashort residual intestine.

DISCUSSION

SBS, the spectrum of malabsorption that occurs after resection or loss of a major portion of the small intestine for congenital or acquired lesions, is the most common cause of intestinal failure in children (10). After intestinal resection, the residual small bowel undergoes intestinal adaptation with gradual improvement of nutrient absorption. Adaptation may take several months or years to complete, and up to 65% of children with SBS will achieve nutritional independence from PN (11). During this time, patients with SBS are either partially or totally dependent on PN. PNALD is the most common complication in children with SBS, occurring in 67% of patients with 25% progressing to end-stage disease (2,4). A number of components of PN solutions have been implicated in the development and acceleration of PNALD, including excess energy (hypercaloric), excess carbohydrates, amino acid content (notably methionine excess), and trace elements such as manganese (12).

TABLE 3. *Biochemical markers for 9 patients with resolution of hyperbilirubinemia*

	Normal	Initiation of therapy	Resolution of hyperbilirubinemia	*P*
Serum albumin, g/L	32–56	30.0 (5.7)	37.11 (2.7)	0.004
ALT, units	0–40	215 (99.6)	92.6 (52.5)	0.032
AST, units	0–45	324.8 (149.4)	114.44 (48.0)	0.002
γ-Glutamyl transferase, units	0–45	173.7 (158.6)	257.8 (234.2)	0.369
International normalized ratio	0.8–1.2	1.18 (0.2)	1.28 (0.2)	0.246

Values are normal range or mean (standard deviation). The *P* value is from the paired *t* test comparing the measure at the start of treatment and at the time of resolution of hyperbilirubinemia.

Intravenous lipids are a critical component of PN solutions that provide essential fatty acids and dense calories; however, fat emulsions have also been implicated as a significant cause of PNALD (13,14). Although Colomb et al (14) have shown that elimination of the fat can result in reversal of PNALD, such a strategy may be inappropriate for infants due to concerns about fatty acid deficiencies.

The precise mechanisms by which fat emulsions contribute to PNALD are not well understood, although there is emerging evidence that the long-chain polyunsaturated fatty acids (LCPUFAs) within the soy-based lipid emulsions play a crucial role in the pathogenesis of PNALD (7,8,15). The main LCPUFAs are ω6FA and ω3FA, which share metabolic pathways and thus interact with each other through a complex system involving dietary substrate availability, competition for the same metabolic enzymes for synthesis and membrane incorporation, and powerful negative feedback of the end products (16). As a result, active ω3FAs interfere with metabolization of the ω6FA arachidonic acid, leading to a downregulation of inflammatory eicosanoids (17). Thus, the ratio of ω6FA to ω3FA (n6:n3 ratio) fatty acids is an important factor in the regulation of inflammation. The optimal ratio of n6:n3 for immunomodulation is proposed to be between 1:1 and 4:1 (18,19).

Soy-based lipid emulsions have been the mainstay of PN since it was established some 30 years ago, and contain predominantly ω6FAs with a n6:n3 ratio of 5.5:1. Intralipid contains ω3FAs in the form of α-linolenic acid, but infants have limited capacity to convert this acid to the biologically active ω3FAs (docosahexanoic and eicosapentaenoic acid). Intralipid does not provide a substantial and utilizable source of ω3FAs in the infant (20,21). In contrast to PN solutions containing predominantly ω6FAs, those which are composed of ω3FAs in addition to ω6FAs have a number of beneficial effects in terms of prevention and treatment of PNALD. First, the addition of ω3FA provides an alternate energy source to plant-based lipids, and thus allows the reduction of the overall dose of phytosterols, which have been demonstrated to impair bile flow (15). Second, ω3FAs have a further beneficial impact on bile flow, possibly by altering the composition of the biliary canalicular membrane and by eicosanoid-mediated mechanisms (15,22). Third, ω6FAs have been implicated in the development of hepatic steatosis, which is 1 of the early hallmarks of PNALD (23). Fourth, administration of fish oil–based lipids has been demonstrated to reverse hepatic steatosis in both PN and non-PN models of hepatic steatosis (24). Finally, addition of ω3FA to the diet results in a relative decrease in ω6FA, and a shift from a predominantly proinflammatory eicosanoid profile to a more modulated profile with increased anti-inflammatory mediators (25). This shift in inflammatory mediators may have important implications in terms of the progression of hepatitis and resultant fibrosis in response to the initial cholestatic and steatotic insult.

Clinical experience with ω3FAs in SBS is limited but dramatic, and has the potential to fundamentally alter the management of infants with this condition. The published evidence is limited to reports from Boston Children's Hospital staff outlining their experience with Omegaven (7,8). Overall, their results have demonstrated the safety and efficacy of Omegaven as a sole lipid source in causing reversal of PNALD. In the most recent publication, 11 of the 18 (61%) patients treated with Omegaven demonstrated resolution of cholestasis (serum direct bilirubin $\leq$2 mg/dL [34 μmol/L]) while receiving Omegaven, with an additional 5 patients demonstrating resolution of cholestasis with PN cessation (8).

This report describes our initial experience with Omegaven in the treatment of children with SBS and PNALD, all of whom were undergoing evaluation or were listed for transplantation. Our initial results are encouraging, with 9 (75%) of the children demonstrating complete resolution of hyperbilirubinemia and having been removed as candidates for liver transplantation. Although our study is limited by the lack of a comparison group, these results represent a dramatic change in the outcome of children with SBS and PNALD, for whom listing for liver-intestinal transplantation meant either transplantation or death with recovery rarely ever occurring. The remaining 3 children did not demonstrate resolution of hyperbilirubinemia, with 2 showing progression of PNALD and 1 demonstrating stable PNALD. The reasons for the lack of resolution in these children are unknown, although both children who demonstrated significant progression of disease have experienced several subsequent septic episodes that were temporally related to increasing hyperbilirubinemia following an initial decline. Whether these episodes are causative in terms of the progression of liver disease or a consequence thereof remains uncertain. In addition, there were other patients in this series with sepsis who did not have progressive liver dysfunction, so the implications of this observation remain unclear. In the remaining patient who demonstrated stable disease for a period of 32 weeks before transplantation, we feel that based on our prior experience (11,26), Omegaven slowed the rate of progression of his liver disease.

Although our data in terms of resolution of hyperbilirubinemia are encouraging, there was still evidence of hepatic inflammation based on persistent elevations in ALT, AST, and γ-glutamyl transferase levels in our patients at the time of resolution of hyperbilirubinemia. It is noteworthy that both the AST and ALT were significantly lower following treatment. This likely reflects variation in the temporal trends with respect to recovery of various hepatic markers. Based on our clinical assessment, as well as the subsequent follow-up period, we have not demonstrated any evidence of a substantive

ongoing process, although we acknowledge that normalization of hyperbilirubinemia does not necessarily imply complete resolution of PNALD.

It is important to acknowledge that the median time to resolution of hyperbilirubinemia (24 weeks) in our study was longer than the 9.4 weeks reported by Gura et al (8). In their group, the median starting serum direct bilirubin was 5.4 mg/dL (interquartile range [IQR] 3.4–7.7 mg/dL). The corresponding values in our study were 8.1 mg/dL (IQR 5.2–10.6 mg/dL). We believe that the time to resolution in our series is longer because our patients had more advanced PNALD. In addition, Gura et al used an endpoint of direct bilirubin 2 mg/dL (34 μmol/L) or less, whereas our endpoint was 0 μmol/L. Finally, the follow-up in the Gura et al series was limited, with no more than 7 data points being available for any time period beyond 20 weeks of treatment. At the end of this period, there were still patients who had a serum direct bilirubin greater than 0 mg/dL. This contrasts with our data, which demonstrate sustained resolution of hyperbilirubinemia with a median follow-up of 31 weeks since resolution. This highlights the robustness of the treatment response.

The differences in time to resolution could be explained by the different dosing strategies that were used. Whereas Gura et al have adopted an approach of using Omegaven as a sole lipid source in PN (7,8), we have mixed Omegaven with Intralipid. Whereas the group in Boston provided 1 g/kg of Omegaven, we provide 1 g/kg of Intralipid and 1 g/kg of Omegaven with an overall n6:n3 ratio of between 1:1 and 2:1. Such a ratio is within the optimal range for anti-inflammatory effect (18,19) and approximates the composition of breast milk, and we believe that such a balanced lipid mix makes more sense physiologically than a lipid that is composed entirely of either predominantly ω6FA or ω3FA. Furthermore, although the limited available short-term evidence does not support any concerns with respect to coagulopathy or clinically significant essential fatty acid deficiency (8,27), it is also important to consider the potential long-term consequences on growth and neurocognitive function of lipid compositions with a predominant fatty acid source, given the importance of both ω6FA and ω3FA on growth and development (28,29).

Despite our views on the benefits of both ω6FA and ω3FA in the diet, we adopted a flexible approach given that the optimal strategy is unknown and we were using this novel therapy as part of a compassionate release salvage protocol and not as a formal research study. All of the children were started on a run-in phase consisting of 1.5 g/kg of Intralipid and 0.5 g/kg of Omegaven for 1 week. This was done to ensure tolerability of Omegaven. In 10 of the cases, the dose was then adjusted to 1 g/kg of Intralipid and 1 g/kg of Omegaven. In 6 of these cases (3 who ultimately underwent transplant and 3 who ultimately had resolution of hyperbilirubinemia), Intralipid was discontinued. The decision to stop Intralipid was not based on specific laboratory criteria but rather on the basis of the clinical judgment of our multidisciplinary team that treatment response was either inadequate or that there was significant disease progression. The remaining 4 of the 10 patients who were treated with a combination of Intralipid and Omegaven had resolution of hyperbilirubinemia while receiving this combination. In 2 cases, the child was treated solely with Omegaven (1 g/kg) following their initial run-in phase. The reasons for this were in 1 case because of an 80-μmol/L (4.71 mg/dL) increase in bilirubin during the initial run-in phase and, in the second case, because of clinical concern that the patient's serum-conjugated bilirubin of 84 μmol/L (4.94 mg/dL) underestimated the severity of the liver disease. Both of these patients demonstrated resolution of hyperbilirubinemia. Given success with various regimens, we firmly believe that the optimal dosing strategy remains to be determined. Neither our data (75% overall success) nor that of Gura et al (61% resolution while taking Omegaven) (8) provide evidence for the relative efficacy of a particular strategy. As such, we believe that well-controlled animal and human studies are needed to make these determinations, considering both short- and long-term implications.

Even when the Omegaven is administered with Intralipid, the total lipid dose is 2 g/kg, which is on the low end of our typical PN lipid dose of 2 to 3 g/kg. As such, it could be argued that the resolution of the PNALD can be explained on the basis of an absolute reduction in PN lipid dose, rather than administration of an alternate lipid source. Although we acknowledge that a portion of the treatment response may be related to reduction in lipid dose, based on the dramatic resolution in hyperbilirubinemia, which is inconsistent with previous clinical experience, we firmly believe that the major factor resulting in resolution of PNALD is the addition of ω3FA to the PN solution. The other potential confounder is weaning of the PN. Although there was significant variability in change in enteral tolerance, there was only a median of 10% increase in enteral tolerance in our 9 patients who resolved completely. Two of these patients continue to have 0% enteral tolerance. Resolution of advanced cholestasis in this setting is highly unusual based on our historical experience. As such, we do not believe that the outcome can be explained solely on the basis of improved enteral tolerance.

We have long held the view that liver disease may hinder intestinal adaptation in children who anatomically have the capacity to adapt, and Omegaven may ultimately facilitate adaptation by allowing for increased time for adaptation free of liver disease. We believe that this should lead to an increase in the number of children with SBS who will eventually adapt completely. We acknowledge, however, that there are children who do not have a capacity to adapt and will ultimately need an intestinal transplant to achieve independence from PN.

We view the role of Omegaven in these children as permitting them to grow free of PNALD or with more stable disease to a larger size, at which time their chances of receiving an intestinal allograft are improved.

Although it is early in the experience, we believe that parenteral ω3FAs have the potential to fundamentally alter the paradigm of neonatal SBS from one of early death or transplantation from liver failure to a more chronic disease. With this improvement, more children with SBS should achieve full enteral tolerance and those who do not have the capacity for intestinal adaptation should be able to survive and receive an intestinal graft when older. Research is still needed to further elucidate the mechanism of action and to define the optimal dose, timing, and manner of administration. Although our results suggest that Omegaven shows significant promise in reversing advanced PNALD in infants with intestinal failure, the goal is not salvage therapy for PNALD but its prevention, and we are actively pursuing such a strategy. These results also may have important implications for the management of adults with advanced PNALD.

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