Fish Oil Emulsion Reduces Liver Injury and Liver Transplantation in Children with Intestinal Failure-Associated Liver Disease: A Multicenter Integrated Study

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Disclosures

- Kathleen Gura
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  - received research support from: Northsea Therapuetics, Otsuka Pharmaceutical Company, Alcresta, and Fresenius Kabi
  - special government employee: FDA Pharmacy Compounding Advisory Committee
  - patent/Royalties for Omegaven

- Mark Puder
  - consultant for: Pronova/BASF, Northsea Therapuetics
  - received research support from: Northsea Therapuetics, Otsuka Pharmaceutical Company, Alcresta, and Fresenius Kabi
  - patent/Royalties for Omegaven

- Kara Calkins
  - consultant for: Fresenius Kabi, Mead Johnson, and Baxter
  - received research support from Fresenius Kabi

- Muralidhar Premkumar
  - consultant for: Fresenius Kabi
Background

- Infants and children receiving prolonged courses of parenteral nutrition (PN) containing soybean oil lipid emulsions (SOLE) have been shown to be at risk for developing liver disease.
- Replacing this lipid emulsion with one that is purely fish oil (FOLE) may be beneficial in reversing this complication.
- Unless PN is discontinued, cholestasis can progress from fibrosis to cirrhosis and death from end-stage liver disease.
- The Pediatric Intestinal Failure Consortium noted a 74.4% incidence of IFALD in children with intestinal failure, with a mortality rate of 27% and a liver transplant rate of 26%.
- SOLE have been linked with IFALD, possibly owing to their phytosterol, high omega-6 fatty acid, and low vitamin E content.
Objective

To compare the aspartate aminotransferase to platelet ratio index, liver transplantation, and mortality rates between children with intestinal failure-associated liver disease who received fish oil lipid emulsion (FOLE) or soybean oil intravenous lipid emulsion (SOLE).
Study design

- Multisite, retrospective study comparing FOLE (n=189) to SOLE subjects (n=73)
- FOLE subjects received open-label FOLE (1 g/kg/d) until IFALD resolved or parenteral nutrition was stopped
- Historical control subjects received SOLE (up to 3 g/kg/d)
Study End Points

- Time to resolution of cholestasis (defined as achieving a DB of <2 mg/dL)
- Number of patients achieving resolution of cholestasis
- Time to liver transplantation
- Number of patients undergoing liver transplantation
- Time to death
- Number of patients who die
- Biochemical markers of liver injury
  - APRI score
  - Direct bilirubin
  - AST
  - Alanine aminotransferase (ALT)
- Adverse events
  - Sepsis events
  - Catheter-related bloodstream infection
- Pediatric End-stage Liver Disease (PELD) score used to estimate disease severity
  - Calculated post hoc for patients who underwent liver transplantation at the time of listing
Results
### Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Categories</th>
<th>FOLE (n = 189)</th>
<th>SOLE (n = 73)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>109 (57.7)</td>
<td>43 (58.9)</td>
<td>.8897</td>
</tr>
<tr>
<td>White race</td>
<td>119 (63.0)</td>
<td>37 (50.7)</td>
<td>.2799</td>
</tr>
<tr>
<td>Unknown race</td>
<td>39 (20.6)</td>
<td>23 (31.5)</td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>30.5 (26.0 to 35.0)</td>
<td>33.0 (28.0 to 36.0)</td>
<td>.0350</td>
</tr>
<tr>
<td>Postmenstrual age (weeks)</td>
<td>41.0 (36.0 to 52.0)</td>
<td>38.0 (34.0 to 43.0)</td>
<td>.0021</td>
</tr>
<tr>
<td>Body weight, Z-score†</td>
<td>-1.48 (-2.55 to -0.63)</td>
<td>-1.30 (-2.03 to -0.56)</td>
<td>.1597</td>
</tr>
<tr>
<td>Height/length, Z-score†</td>
<td>-1.86 (-3.04 to -0.88)</td>
<td>-1.81 (-2.89 to -1.16)</td>
<td>.4690</td>
</tr>
<tr>
<td>Head circumference, Z-score†</td>
<td>-1.58 (-2.71 to -0.62)</td>
<td>-1.19 (-1.62 to -0.07)</td>
<td>.0156</td>
</tr>
<tr>
<td>DB (mg/dL)</td>
<td>5.80 (3.50 to 9.00)</td>
<td>3.00 (2.20 to 4.40)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>133.53 (77.84 to 209.58)</td>
<td>70.66 (28.74 to 133.53)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>88.02 (43.11 to 185.63)</td>
<td>35.33 (17.96 to 82.63)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Comparison of median APRI score for FOLE recipients and SOLE recipients at baseline, resolution of cholestasis, and end of study.
# ANCOVA Analysis of Changes Over Time in Liver Function Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Time point (observations)</th>
<th>Resolution of cholestasis†</th>
<th>End of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>DB (mg/dL), n</td>
<td>247</td>
<td>236</td>
<td></td>
</tr>
<tr>
<td>FOLE</td>
<td>-1.99 [-3.08 to -0.91]</td>
<td>-2.55 [-3.72 to -1.39]</td>
<td></td>
</tr>
<tr>
<td>SOLE</td>
<td>3.95 [2.07 to 5.84]</td>
<td>4.34 [2.36 to 6.33]</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>-5.95 [-8.16 to -3.73]</td>
<td>-6.89 [-9.25 to -4.54]</td>
<td></td>
</tr>
<tr>
<td>$P$ value§</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>ALT (U/L), n</td>
<td>214</td>
<td>207</td>
<td></td>
</tr>
<tr>
<td>FOLE</td>
<td>4.19 [-41.32 to 49.70]</td>
<td>-13.77 [-61.68 to 33.53]</td>
<td></td>
</tr>
<tr>
<td>SOLE</td>
<td>125.15 [46.71 to 204.19]</td>
<td>128.74 [48.50 to 208.98]</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>-121.56 [-213.17 to -29.34]</td>
<td>-142.51 [-236.53 to -48.50]</td>
<td></td>
</tr>
<tr>
<td>$P$ value§</td>
<td>.0098</td>
<td>.0031</td>
<td></td>
</tr>
<tr>
<td>AST (U/L), n</td>
<td>183</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>FOLE</td>
<td>-13.17 [-76.65 to 50.30]</td>
<td>-23.95 [-91.62 to 43.11]</td>
<td></td>
</tr>
<tr>
<td>SOLE</td>
<td>317.96 [173.65 to 461.68]</td>
<td>329.34 [180.84 to 477.84]</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>-331.14 [-488.62 to -173.05]</td>
<td>-353.29 [-517.37 to -189.82]</td>
<td></td>
</tr>
<tr>
<td>$P$ value§</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>
Percentage of patients with resolution of cholestasis, liver transplantation, and who died by the end of the study

FOLE: 122/189
SOLE: 12/73

Cholestasis Resolved

FOLE: 8/189
SOLE: 9/73

Liver Transplant

FOLE: 24/189
SOLE: 11/73

Died

P < .0001
P = .0245
NS
Liver Transplantation

- Fewer FOLE recipients underwent liver transplantation compared with SOLE recipients (4% vs 12%; \( P = .0245 \))
- Mean PELD score was marginally higher for FOLE recipients than for SOLE recipients (25.9 vs 20.0; \( P = .0612 \))
- The estimated median time to liver transplantation was 79.0 weeks (95% CI, 55.7 to \(-\)) for SOLE recipients and could not be calculated owing to lack of events for FOLE recipients (\( P = .0310 \))
Kaplan-Meier Survival Estimates

Time to resolution of cholestasis for FOLE recipients compared with SOLE recipients.

Time to liver transplantation for FOLE recipients compared with SOLE recipients.

Time to death for FOLE recipients compared with SOLE recipients.
Mortality

- The incidence of death was similar for FOLE and SOLE recipients (13% vs 15%; P = .6858)
- FOLE recipients who died
  - More premature at birth (median gestational age 26 weeks vs 33 weeks; P = .0020)
  - Had higher DB levels at baseline (6.2 mg/dL vs 3.6 mg/dL; P = .0505)
- Cause of death similar for both groups
  - Primarily of respiratory and cardiac disorders
  - 4% FOLE recipients died because of general disorders, including multiple organ dysfunction syndrome,
  - 4% SOLE recipients died because of their hepatobiliary disorders
  - None of the deaths in FOLE recipients were considered related to the study treatment.
  - 3 deaths in SOLE group considered related to treatment
    - respiratory failure (1 patient)
    - hepatic failure-associated events (3 events in 1 patient and 1 event in 1 patient)
Regression analysis for the estimated probability of resolution of cholestasis, liver transplantation, and death by baseline DB for FOLE recipients compared with SOLE recipients.
Central Line Infections and Central Line Sepsis

- The number of patients having a central line infection/sepsis was greater in the FOLE group.
- Among FOLE recipients, 76 of 189 patients (40.2%) experienced a central line infection or central line sepsis in comparison with 25 of 73 SOLE recipients (34.2%) (P = .3987).

Key Point
- when analyzed by frequency per patient-year of exposure,
  - the number of central line infections or sepsis events was significantly greater in the SOLE group (P = .0007).
  - SOLE recipients had approximately 2 central line infections or central line sepsis events per year (56 events per 27.9 patient-years).
  - Only 1.14 events per year (168 events per 146.8 patient-years) in the FOLE group.
Conclusions

- FOLE recipients in comparison to SOLE:
  - Higher rate of cholestasis resolution
  - Lower aspartate aminotransferase to platelet ratio index
  - Fewer liver transplants compared with SOLE

- This study demonstrates that FOLE may be the preferred parenteral lipid emulsion in children with intestinal failure-associated liver disease when DB reaches 2 mg/dL
Thank you to my collaborators

Mark Puder MD, PhD

Kara L. Calkins, MD

Murali Premkumar, MD
The true collaborators!
Thank you!!!