FAMILIAL CHYLOMICRONEMIA SYNDROME (FCS): MEDICAL NUTRITION THERAPY GUIDELINES FOR PATIENTS AND HEALTHCARE PROVIDERS

Lori Alexander, Lauren Williams, Lori Welstead, Kathy Rhodes, Wahida Karmally and Lindsey Sutton on behalf of the FCS patients and their families

BACKGROUND

What is FCS?

- **Background:**
  - Rare autonomic recessive disorder (autosomal recessive disease)
  - Incidence: 1:10,000, generally presenting every 3-5 weeks
  - Seven levels of titer in plasma Tg, generally responsive to lipid-lowering therapies
  - Caused by null-base mutation in LPL

Clinical Expression/Risk:

- Plasma lipid profile
- Plasma triglyceride levels

Goals and Objectives:

- Patients with FCS struggle with many aspects of the need to follow a restrictive diet, not only in locating information on guidelines
- Decreased quality of life (QoL)
- Hepatosplenomegaly
- Recurrent acute pancreatitis (AP)
- Pancreatic insufficiency
- Increased metabolic activity
- Depression/anxiety
- Fatigue may impact eating habits and ability to cook or shop for food

METHODS

Patients with FCS struggle with many aspects of the need to follow a restrictive diet, not only in locating information on guidelines and adherence strategies, but also with impact on social interactions and their well-being.

The Registered Dietitian Nutritionist (RDN) Working Group

- RDAs for a new working group meeting to discuss and to come to consensus on the dietary guidelines for patients with FCS
- Included in the group was a patient with FCS
- Individual presentations by all faculty members were compiled to produce dietary guidelines for patients with FCS across the lifespan
- Goals and Objectives:
  - Establish dietary guidelines for patients with FCS across the lifespan
  - Publication of guidelines
  - Create educational dietary resources for HCPs

RECOMMENDATIONS & DISCUSSION

FCS: Treatment is Lifelong

- Current treatment is a lifelong extremely restrictive low-fat diet, consisting of >20 grams fat or 15% total calories, exact fat intake goals should be provided on an individual basis upon estimated needs of the patient
- MCT oil
- Short-term target treatment goal: immediate prevention/treatment of pericarditis
- Avoid oral estrogens, diuretics, isotretinoin, glucocorticoids, soluble vitamins and micronutrients

Dietary Management of FCS in Pediatrics

- Very low fat diet (10-15% of calories from fat)
- Limit simple carbohydrates: limit total carbohydrates
- Low in simple carbohydrates: limit total carbohydrates
- Add foods to increase:
  - Foods to increase:
    - Avoid concentrated sweet, including corn syrup solids
    - Proteins: casein, soy protein, milk, and whey protein
    - Oils: olive, peanut, corn, safflower

Dietary Management of FCS in Adults

- Very low fat diet (10-15% as tolerated)
- Low in simple carbohydrates: limit total carbohydrates
- Foods to avoid:
  - Foods to avoid:
    - Alcohol
    - Coffee
    - Tea
    - Tobacco
- Dietary therapy with MCT oil

REFERENCES

Alexander, MS, RDN, COSD, CSSD, MEd, CENT, Diabetes Educator, Medical Nutrition Therapist, Georgia Diabetes Care Center, Marietta, GA, USA, 1 Williams, MD, PhD, Division of Gastroenterology, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA, 2 Welstead, MS, RD, LDN, SD, Division of Nutrition Care, Texas Children's Hospital, Houston, TX, USA, 3 Sutton, of the FCS Foundation

Sample Comparison of Two Low Fat Formulas, Term Human Milk, and a Standard Infant Formula

<table>
<thead>
<tr>
<th>Formula</th>
<th>LMF1 12% MCT</th>
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<th>Human Milk</th>
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<tr>
<td>Fat (% kcal)</td>
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<td>20.8 (48)</td>
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<td>Carbohydrate (% kcal)</td>
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<tr>
<td>Carbohydrate (g/100mL)</td>
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<td>0.3 (39)</td>
<td>0.9 (56)</td>
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<tr>
<td>Calculated MDA (kcal/mL)</td>
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Characterizing Familial Chylomicronemia Syndrome: Baseline data of the APPROACH Study

Dirk Blom, MD, Vicki Alexander, PhD, Andres Digenio, MD, Seth Baum, MD, Linda Hemphill, MD, Raul Santos, MD, Ewa Prokopczuk, MD, Ovidio Muniz-Grijalvo, MD, Joseph Witztum, MD, Daniel Gaudet, MD, (Cape Town, South Africa)

Lead Author’s Financial Disclosures: Advisor: IONIS/Akcea Therapeutics. Clinical trial investigator: IONIS/Akcea Therapeutics

Study Funding: Yes

Study Funding: Funding for study was provided by IONIS Pharmaceuticals /Akcea Therapeutics

Background/Synopsis: Familial Chylomicronemia Syndrome (FCS) is a rare, recessive genetic disorder caused by mutations in Lipoprotein Lipase (LPL) or genes required for LPL functionality. FCS is characterized by hyperchylomicronemia, recurrent abdominal pain, hepatosplenomegaly and recurrent episodes of acute pancreatitis that may result in pancreatic insufficiency. There are no FDA approved treatments for FCS and patients are managed with a low-fat diet. Due to the rarity of FCS there are few case series describing phenotypic variability in this disorder.

Objective/Purpose: To describe demographic and clinical characteristics of adult FCS patients enrolled in a clinical trial.

Methods: We analyzed baseline data from 67 patients with FCS, participating in a Phase III study of volanesorsen (apoC-III antisense oligonucleotide).

Results: Sixty-seven patients with a mean age of 46±13 years were enrolled. In 54 patients (80%) the diagnosis was confirmed genetically with LPL mutations accounting for 41 (81%) cases. The median age (P25, P75) at diagnosis was 27 (15, 36) years. Fifty four percent were female and 81% were Caucasian with a mean body mass index of 24.9±5.7 kg/m². Median fasting TG (P25, P75) were 2012 (1247, 3117) mg/dL despite 43% of patients receiving fibrates, 27% fish oils and 21% statins. Eruptive xanthomas and lipemia retinalis were identified in 15 (22%) and 14 (21%) of patients, respectively. Forty-nine patients (73%) had a documented history of acute pancreatitis and among those, 27 patients experienced 83 pancreatitis events within the past 5 years. Twenty five percent of patients (17 out of 67) reported abdominal pain events during the 6-8 week screening period. Magnetic resonance imaging demonstrated that liver and splenic volumes were increased and that splenic volume had a mild inverse correlation with platelet counts (r=-0.1200, p=0.0052). Postprandial TG clearance was severely impaired (Figure).

Conclusions: Our data confirm that TGs remain significantly elevated in most FCS patients despite dietary restrictions and TG-lowering therapies and that FCS is frequently complicated by acute pancreatitis. A relatively late age of diagnosis suggests a likely under diagnosis and appreciation of this rare genetic disorder.

Familial Chylomicronemia Syndrome (FCS): Medical Nutrition Therapy for Patients and Providers

Lori Alexander, MS, RDN, CCRC, Wahida Karmally, DrPH, MS, RDN, Kathy Rhodes, PhD, RD, Lori Welsted, MS, RD, LDN, Lauren Williams, MCN, RD, LD, Lindsey Sutton, (Jacksonville, FL)

Lead Author’s Financial Disclosures: None

Study Funding: Akcea Therapeutics supported the expert group with conference calls and a live meeting, and all content was developed independently by the expert committee.

Background/Synopsis: FCS is a rare autosomal recessive disorder due mainly to loss of function mutations of lipoprotein lipase. This results in severe elevation of triglycerides (TG) and massive accumulation of chylomicrons in plasma, often leading to pancreatitis. This under-diagnosed disorder causes decreased quality of life (QoL) and increased ER visits and hospitalizations. Many FCS patients live in isolation, experience employment difficulties and have trouble socializing due to its consequences.

Objective/Purpose: An unmet need came out of an FCS expert committee of Registered Dietitians/Nutritionists (RDNs) and patients, sharing challenges and adherence to dietary restrictions, meeting nutrient requirements and improving QoL. The aim was to share best practices, and ultimately provide tools and relevant resources to support patients, caregivers and healthcare professionals, and raise awareness of the dietary impact of managing the disease.

Methods: RDNs were interviewed to assess their expertise and interest in joining the expert group. Each RDN was assigned a topic in their area of expertise for the development of the consensus report. A patient with FCS was also included in the group to provide a personal perspective of the challenges of living with FCS. The report included patient-centered nutrition recommendations to optimize nutritional needs to manage and prevent complications of FCS. The report also provided resources for healthcare professionals. Topic-specific presentations were developed for future education.

Results: The RDN expert committee incorporated topic-specific presentations into a consensus report on diet and FCS. Topics provided current information on FCS, pancreatitis, implementing current nutrition recommendations,
supporting patients with adherence to a very low fat diet, pediatric management of FCS, pharmacologic therapies available and in development, and personal experiences of a patient diagnosed with FCS in infancy.

**Conclusions:** This report adds valuable resources to the limited information currently available to assist patients with FCS and healthcare providers. The dissemination plans for this report include submitting a manuscript for publication, developing web-based CEU programs to “Train the Trainer”, employing patient education resources such as recipes and FCS Foundation blog participation, and providing resources for support groups.

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**PCSK-9i Gender Study**

**Debra Friedrich, DNP, FNP-BC, CLS, Paul Ziajka, MD, PhD, FNLA, Sudha Ravilla, MD, ABCL, John Diaz, MD, FAAFP, Ralph Vicari, MD, FNLA, (Bradenton, FL)**

**Lead Author’s Financial Disclosures:** None

**Study Funding:** None

**Background/Synopsis:** Due to residual risk in patients unable to achieve LDL goals with maximum tolerated statin doses, coronary heart disease still remains the leading cause of death in both men and women. In 2015, monoclonal antibody therapy to reduce PCSK9 activity at the surface of the hepatocyte was approved. PCSK9 blocking antibodies can reduce LDL-C up to 70% beyond levels achieved with statin therapies alone.

**Objective/Purpose:** To examine the significance of an observational trend observed in multiple lipid clinic sites that indicate a more robust drop in LDL-C in men verses women with both alirocumab and evolocumab.

**Methods:** A retrospective chart review was conducted with data collected from several lipid clinics in Florida. A one page data collection form was developed during the initial pilot study. The primary endpoint was to quantify gender differences in LDL-C lowering in PCSK-9 inhibition (aggregate, alirocumab and evolocumab). Secondary endpoints included (1) gender differences in LDL-C response to PCSK-9 inhibition (aggregate, alirocumab and evolocumab) in patients on non-zero vs. zero tolerated statin dose (2) gender differences in LDL-C response to PCSK-9 inhibition (aggregate, alirocumab and evolocumab) in patients based on age and (3) gender differences in LDL-C response to PCSK-9 inhibition (aggregate, alirocumab and evolocumab) in patients based on baseline LDL-C levels.

**Results:** Results and Conclusions: Data was collected from 5 lipid clinics with a sample size of 97 patients. Conclusions from the 4 data analysis revealed the following: (1) Men have a statistically significantly greater LDL-C reduction than women. LDL-C Reduction (% from baseline):
(2) Except for the eldest cohort, the trend for men getting a greater reduction across age quintiles is consistent. (note that the n’s in each group are low making it difficult to reach statistical significance) (3) Regardless of baseline LDL the men / women differential persists, although the n’s in each group are too small to reach statistical significance. (4) The differences in LDL-C lowering between men and women are due to those patients on concommitent statin therapy.

**Conclusions:** Implications: Should a more aggressive approach to lipid management with PCSK9-I be considered in women who show a less robust response to therapy. Will these gender results be relevant in outcome studies available later this year?

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**Familial Chylomicronemia Syndrome (FCS) Patients Recruited to the APPROACH Trial of Volanesorsen Therapy are Representative of Subjects with FCS**

**Daniel Gaudet, MD, Dirk Blom, MBchB, PhD, Eric Bruckert, MD, PhD, Erik Stroes, MD, John Kastelein, MD, PhD, John Kane, MD, PhD, Mary Malloy, MD, Philippe Moulin, MD, Kjetil Retterstol, MD, PhD, Steve Hughes, MD, Andres Digenio, MD, Joseph Witztum, MD, Sam Tsimikas, MD, (Chicoutimi, QC)**

**Lead Author’s Financial Disclosures:** Dr. Gaudet has received research grant support from FH Canada, Aegerion (Novelion Therapeutics), Amgen, Akcea, AstraZeneca, Chiesi, Cymabay, DalCor Pharma, Esperion, GlaxoSmithKline, Gempshire, Ionis, Pfizer, Regeneron and Sanofi, and has served as a consultant for Amgen, Aegerion, Akcea, Chiesi, Cymabay, Ionis, Regeneron, Sanofi and Unquire. Dr. Gaudet was also an investigator for the APPROACH study.

**Study Funding:** APPROACH study was funded by Akcea Therapeutics a subsidiary of IONIS pharmaceuticals

**Background/Synopsis:** FCS is a rare autosomal recessive disease due to markedly reduced lipoprotein lipase activity. Because of lack of effective therapy, FCS is associated with a greater burden of disease and mortality compared with other hypertriglyceridemic disorders. A seminal pilot study demonstrated that inhibiting apoC-III using the antisense oligonucleotide volanesorsen was a potentially highly effective therapy. The APPROACH Trial