TALKING DIRECTLY TO PATIENTS TO UNDERSTAND THE CLINICAL AND PSYCHOSOCIAL BURDEN OF LIVING WITH FAMILIAL CHYLOMICRONEMIA SYNDROME

Alan Brown, Joyce Ross, Andrew Hsieh, Alan Gilstrap, Karren Williams, Andres Gelrud

Akcea Therapeutics, Cambridge, MA, USA

AKCEA THERAPEUTICS™

A subsidiary of Ionis Pharmaceuticals, Inc.

Click for Kiosk Menu

ABSTRACT

Background: FCS is a rare, inherited lipid disorder characterized by severely high levels of triglycerides (TGs) and chylomicrons in the plasma. The impact of FCS includes acute physical manifestations (eruptive xanthoma, lipemia retinalis, hepatosplenomegaly) and potentially life-threatening recurrent acute pancreatitis (RAP), which frequently leads to chronic pancreatitis. Patients with FCS often live in fear of RAP and debilitating abdominal pain. There is currently no FDA approved pharmacotherapy. The mainstay is an ultra-low-fat diet (<20g of fat per day) and strict control of lifestyle factors (e.g., avoidance of alcohol and some medications), which is difficult for patients to maintain. Additionally, there is a dearth of information regarding the burden of FCS on quality of life for patients and their caregivers.

Objective: To elucidate the impact of FCS on both patients' and caregivers' quality of life (QOL).

Methods: FCS patients and their respective caregivers were invited to participate in a facilitator-led question and answer panel. Questions related to QOL and psychosocial consequence of FCS.

Results: Ten patients and nine caregivers participated in the patient-advocated directed panel discussion. Mean age of patients in attendance was 42.7 years (Range 26-67yrs). Patients reported 395 combined episodes of pancreatitis with 180 hospitalizations resulting in 1260 days hospitalized. FCS consequences included: Fatty liver disease (80%), cholecystectomy (64%), and diabetes (50%). Patients and caregivers reported that psychosocial manifestations of FCS have limited their ability to perform activities of daily living, including missed work and school. All participants reported fatigue, lack of concentration and cognitive impairment. Caregivers also reported psychosocial stressors.

Conclusion: FCS is a debilitating, chronic disease. No optimal or FDA approved medical therapy is available. An extremely restrictive diet is critical but difficult for patients to follow, limits social interactions, and can reduce QOL. FCS affects many organs including the pancreas, leading to RAP and frequent hospital admissions.

INTRODUCTION

- Familial chylomicronemia syndrome (FCS) (other nomenclature for FCS includes hyperlipoproteinemia type 1, lipoprotein lipase deficiency, lipase D deficiency, familial hyperchylomicronemia, familial chylomicronemia, chylomicronemia syndrome, idiopathic hyperlipemia, Burger-Grutz syndrome[1]), is a rare metabolic disorder that is characterized by the presence of hyperchylomicronemia and severe hypertriglyceridemia[1]
- The most common cause of FCS is loss of or reduced function of lipoprotein lipase (LPL), an enzyme that catalyzes the hydrolysis of TG-rich lipoproteins and the subsequent uptake of TG into peripheral tissue[2,3]
- 10 adult patients with FCS, either clinically or genetically diagnosed, were assembled in a face-to-face patient advisory meeting
  - Patients were asked to qualitatively assess the clinical burden and psychosocial consequences of FCS and the effects of FCS on their quality of life
  - 8 of the 10 patients were accompanied by a spouse or a caregiver who was allowed to provide additional information

RESULTS

- Patient demographics and characteristics are shown in **Table 1**

Table 1. Patient Demographics and Characteristics

n=6 Males; n=4 Females	Median	Range
Current age (years)	48	26-67
Age at symptom onset (years)	15.5	0.125-49
Highest plasma TG value (mg/dL)	10, 500	2,600-21,000
Average plasma TG value (mg/dL)	1,300	600-3,100
Number of AP episodes (n)	34	6-60
Hospitalizations due to AP (n)	17	2-40
Average length of hospitalization (days)	6.5	3-14

AP, acute pancreatitis; TG, triglycerides

Symptoms of FCS

- Symptoms reported by patients with FCS were primarily gastrointestinal, including abdominal pain, nausea, diarrhea, constipation, and bloating
  - Back pain, referred pain, headache, and fever were also reported
  - Abdominal pain and fatigue were the 2 most common symptoms
  - Most patients reported that symptoms have progressed with age, particularly in terms of frequency of events

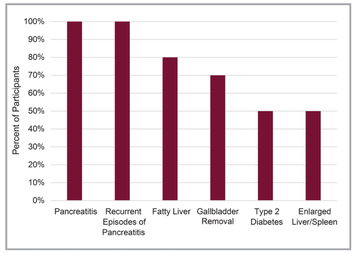
Medical Complications Associated with FCS

- Most common and serious complication of FCS is acute pancreatitis (AP)
- Other commonly reported complications of FCS were fatty liver disease, type 2 diabetes, and liver and/or spleen enlargement (Figure 1)
- Gallbladder had been removed in 7 of 10 patients with FCS, presumably due to misdiagnosis of gallbladder issues as the cause of AP
- 3 patients each with FCS also reported pancreatic damage and memory loss

Medical Complications Associated with FCS *continued*

- Additional potential complications of FCS reported by individual patients included hypokalemia, hypocalcemia, cirrhosis of the liver, hypothyroidism, vitamin and mineral deficiencies, anemia, and gastric issues
- All patients reported experiencing daily nausea and low-level abdominal pain that could quickly worsen and sometimes become debilitating

Figure 1. Medical Complications Associated with FCS

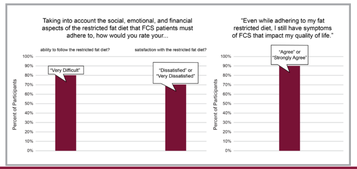


Factors Contributing to Reduced Quality of Life in Patients with FCS (Table 2)

- Low-fat diet
  - Extremely difficult to maintain, particularly when out of the house
  - Affects other members of the household and limits social interactions
  - Patient satisfaction with the diet is very low
  - Patients are not convinced that the low-fat diet reduces the symptoms of FCS

"The most discouraging thing is that we work our butts off to maintain a strict diet and we are still only treading water."

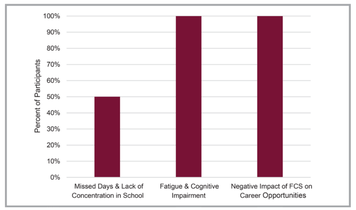
Figure 2. Sentiments Regarding the Restricted Fat Diet for FCS



- Effect of FCS on employment and careers
  - Fatigue and pain sometimes limit job performance
  - Frequent absences can be viewed negatively at promotion time
  - Concerns about diet make travel and attendance at meetings with meals difficult
  - Need for healthcare and insurance limits job opportunities
  - Symptoms of FCS limit ability of patients to train for and perform work in some preferred careers

"I went to college for firefighting but was not able to pursue this career full-time because of fatigue and muscle pain."

Figure 3. Patient-reported Impact of FCS on School and Work



- Effects of FCS on Social Life
  - Caregivers typically report that social life is limited by symptoms, particularly fatigue and dietary/lifestyle restrictions associated with FCS
  - Friends and family do not understand seriousness of FCS
  - Some caregivers have difficulty adjusting to the curtailment of social life that can result from FCS, imposing additional stress on the relationship

"My wife spends a lot of downtime. I don't have any social interactions because of that."

Table 2. Factors Contributing to Reduced Quality of Life in Patients with FCS

Effect of Low-fat Diet
- Compliance with the diet is extremely difficult; particularly when out of the house
- Diet affects other members of the household and limits socialization
- Satisfaction with the diet is very low
- Patients are not convinced that the diet is beneficial for reducing symptoms

Effect of FCS on Jobs and Careers
- Fatigue and inability to concentrate due to pain can limit performance
- Frequent job absences can impede promotion
- Concerns about diet limit the ability to travel on the job
- Need for healthcare and insurance limits job opportunities
- Symptoms of FCS limit ability of patients to train for or perform work in a preferred career

Effect of FCS on Social Life
- Fatigue and dietary lifestyle considerations associated with FCS limit social life
- Failure of friends and family to understand the seriousness of FCS is a major irritant
- Some caregivers have difficulty adjusting to a reduced social life

Effects of FCS on Relationships

- In most cases, patients felt that the shared experience of FCS had drawn couples and families closer together; some patients credited their caregivers with their survival

"Deep down, I know that I wouldn't be around without my wife, even though I don't express this to her."

- Some patients are concerned that the burden imposed on caregivers is too great

"My wife is my rock. But who is the rock for my wife when I am not able?"

- Some caregivers feel socially isolated by the effects of FCS on the spouse

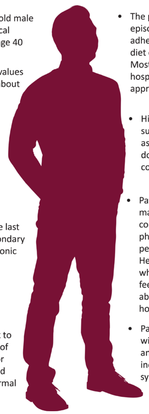
"I can't stay home for 30 years worrying about what you are going to eat."

- Some caregivers have sought outside counseling to help cope with their burden

Hopes for a Future Therapy for FCS

- Both patients with FCS and caregivers were asked what they hoped future FCS therapy would do for them
  - Both expressed hope that a future therapy would reduce the pain and symptoms associated with FCS, improve patient quality of life, and minimize hospitalizations
  - Several patients also expressed a wish for a less stressful, more normal lifestyle that includes socialization and a more normal diet
  - Several patients expressed hope that any future therapy would improve their plasma TG values and treat the underlying disease, not just the symptoms

Profile of Patient with FCS



- Patient is a 46-year-old male who received a clinical diagnosis of FCS at age 40
- Average plasma TG values for this patient are about 1,100 mg/dL
- Patient has fatty liver disease, type 2 diabetes, and has had his gallbladder removed
- Patient has been in constant pain for the last 2 years and has secondary issues related to chronic use of painkillers (eg, constipation)
- Patient would do anything to get back to his previous quality of life. He would like for the pain to cease and to be able to eat normal foods
- The patient has had 40-50 episodes of AP despite adherence to a low-fat diet of less than 10 g/week. Most episodes of AP result in hospitalization for approximately 5 days
- His wife has been supportive and serves as his advocate with doctors and insurance companies
- Patient formerly worked in manufacturing and as a contractor but now is physically unable to perform these jobs. He manages the house while his wife works but feels guilty for not being able to work outside the house
- Patient is dissatisfied with the low-fat diet and believes that it is ineffective for reducing the symptoms of FCS

Limitations of this Report

- Small sample size
- Unstructured, qualitative methodology

CONCLUSIONS

- **FCS and its associated symptoms impose a considerable clinical and psychosocial burden on patients that reduces quality of life and limits employment opportunities**
- **AP is the most serious complication of FCS. AP results in debilitating pain, anxiety, loss of employment, and frequent hospitalizations that disrupt patients' lives**
- **Abdominal pain and fatigue are the most common clinical symptoms associated with FCS and form the constant backdrop of life for every patient with FCS**
- **Much of the psychosocial burden of FCS is associated with the diet and lifestyle changes imposed by this condition, which limit socialization and increase the burden on the family**
- **Patients with FCS want better control of the symptoms of their disease and a more normal lifestyle**
- **There is a serious need for effective and less burdensome ways to control the symptoms of FCS and reduce the clinical and psychosocial burden of this condition**

REFERENCES

1. Genetic and Rare Diseases Information Center. https://rarediseases.info.nih.gov/diseases/6414/hyperlipoproteinemia-type-1. March 8, 2016.
2. Brahm AJ, Hegele RA. *Nat Rev Endocrinol.* 2015;11:352-362.
3. Johansen C, et al. *J Lipid Res.* 2011;52:189-206.
4. Rashid N, et al. *J Clin Lipidol.* 2016; in press.
5. Murphy MJ, et al. *JAMA Intern Med.* 2013;173:162-164.
6. Rare Disease Report. http://fcs.raredr.com. 2014.
7. Jacobson TA, et al. *J Clin Lipidol.* 2015;9:129-169.

ACKNOWLEDGEMENTS

Poster production support was provided by MedVal Scientific Information Services, LLC (Skillman, NJ) and Tracy Reigle/Ionis Pharmaceuticals, Inc. (Carlsbad, CA) and funded by Akcea Therapeutics (Cambridge, MA).

DISCLOSURES

The patient advisory board was funded by Akcea Therapeutics. **Drs Brown and Gelrud** were paid an honorarium for their time at the meeting to serve as faculty at the advisory board.

A Gilstrap, K Williams and A Hsieh are employees of Akcea Therapeutics

J Ross has been/is a consultant for Kameka America and Akcea Therapeutics; speakers' bureau member for KOWA, Astra Zeneca, Amgen, Amarin, Pharma Inc, Sanofi-Aventis, and Regeneron.

A Brown is/has an advisory board member for Ionis Pharmaceuticals/Akcea Therapeutics, Amgen, AstraZeneca, KOWA, Lilly, Merck, Pfizer, and Regeneron; Speakers' bureau member for Amgen, Merck, Regeneron, and Sanofi-Aventis; and received remuneration for participating in this patient advisory board panel as a medical expert.

Methods: This Phase 3 clinical trial enrolled 66 FCS patients with fasting triglycerides ≥8.4 mmol/L (≥750 mg/dL). Participants were randomized 1:1 to 52 weeks of weekly subcutaneous volanesorsen (300mg) or placebo. The primary efficacy endpoint (mean % reduction in plasma triglyceride concentration) was evaluated at 13 weeks.

Results: Mean (SD) baseline triglycerides were 24.9 mmol/L (13.5) (2209 mg/dL [1199]). Week 13 triglycerides decreased by a mean (95% CI) of 77% (-97.4, -55.5) in volanesorsen-treated patients (n=33) and increased by 18% (-4.0, 39.2) in placebo-treated patients (n=33) ($p<0.0001$). This effect was sustained over the 52-week treatment period (-50.1% [-71.4, -28.7]). Volanesorsen-treated patients who reported at least two episodes of pancreatitis in the five years preceding randomization suffered no attacks during the 52-week period ($p=0.02$). A reduction in self-reported abdominal pain intensity was observed in volanesorsen compared to placebo ($p=0.03$). There were no treatment-related renal or liver adverse events. The most common adverse event in the volanesorsen-treated group was injection site reactions (11.8% of all injections). Declines in platelet counts led to 5 early terminations, two of which had platelets <25,000/μl.

Conclusions: Volanesorsen reduced triglycerides, abdominal pain and recurrence of pancreatitis in FCS patients. Changes in platelets require surveillance and are manageable with frequent monitoring of platelet count.

170

The Clinical and Psychosocial Burden of Patients with Familial Chylomicronemia Syndrome

Alan Brown, MD, Joyce Ross, NP, Alan Gilstrap, BS, Andrew Hsieh, PharmD, Karren Williams, PhD, Andres Gelrud, MD, (Park Ridge, IL)

Lead Author's Financial Disclosures: Advisory board member of IONIS Pharmaceuticals, Akcea Therapeutics, Amgen, AstraZeneca, KOWA, Lilly, Merck, Pfizer, and Regeneron; speaker's bureau member of Amgen, Merck, Regeneron, and Sanofi-Aventis; and received remuneration for participating in this patient/caregiver panel as a medical expert.

Study Funding: Akcea Therapeutics, a subsidiary of Ionis Pharmaceuticals, Inc, funded the patient and caregiver panel. Neither patients nor caregivers were paid for their participation.

Background/Synopsis: Familial Chylomicronemia Syndrome (FCS) is a rare, inherited lipid disorder characterized by severely high levels of triglycerides (TGs) and chylomicrons in the plasma. The impact of FCS includes acute physical manifestations (eruptive xanthoma, lipemia retinalis, hepatosplenomegaly) and potentially life-threatening recurrent acute pancreatitis (RAP), which frequently leads to chronic pancreatitis. Patients with FCS often live in fear of RAP and debilitating abdominal pain. There is currently no FDA approved pharmacotherapy. The current mainstay in the management of FCS is an ultra-low-fat diet (<20g of fat per day) and strict control of lifestyle factors (e.g., avoidance of alcohol and some medications), which is difficult for patients to maintain. There is a dearth of information regarding the burden of FCS on quality of life for patients and their caregivers. A panel of patients diagnosed FCS and their caregivers was assembled and surveyed to assess the clinical and psychosocial burden of FCS.

Objective/Purpose: FCS is a rare, inherited lipid disorder characterized by severely high levels of triglycerides (TGs) and chylomicrons in the plasma. The impact of FCS includes acute physical manifestations (eruptive xanthoma, lipemia retinalis, hepatosplenomegaly) and potentially life-threatening recurrent acute pancreatitis (RAP), which frequently leads to chronic pancreatitis. Patients with FCS often live in fear of RAP and debilitating abdominal pain. There is currently no FDA approved pharmacotherapy. The mainstay is an ultra-low-fat diet (<20g of fat per day) and strict control of lifestyle factors (e.g., avoidance of alcohol and some medications), which is difficult for patients to maintain. Additionally, there is a dearth of information regarding the burden of FCS on quality of life for patients and their caregivers. Objective: To elucidate the impact of FCS on both patients' and caregivers' quality of life (QOL).

Methods: FCS patients and their respective caregivers were invited to participate in a facilitator-led question and answer panel. Questions related to QOL and psychosocial consequence of FCS.

Results: Ten patients and nine caregivers participated in the patient-advocated directed panel discussion. Mean age of patients in attendance was 42.7 years (Range 26-67yrs). Patients reported 395 combined episodes of pancreatitis with 180 hospitalizations resulting in 1260 days hospitalized. FCS consequences included: Fatty liver disease (80%), cholecystectomy (64%), and diabetes (50%). Patients and caregivers reported that psychosocial manifestations of FCS have limited their ability to perform activities of daily living, including missed work and school. All participants reported fatigue, lack of concentration and cognitive impairment. Caregivers also reported psychosocial stressors.

Conclusions: FCS is a debilitating, chronic disease. No optimal or FDA approved medical therapy is available. An extremely restrictive diet is critical but difficult for patients to follow, limits social interactions, and can reduce QOL. FCS affects many organs including the pancreas, leading to RAP and frequent hospital admissions.