Limb Girdle Muscular Dystrophies (LGMD)
FDA Patient-led Listening Session

October 20, 2020

Background: Limb Girdle Muscular Dystrophies (LGMDs) are a group of muscular dystrophies, each caused by mutations in one of approximately 30 different genes critical to muscle function. Thus, at a genetic level, LGMD is not a single disease, but a group of many diseases (often referred to as subtypes). LGMDs are all genetic in origin, and by definition, have autosomal inheritance (usually recessive, but sometimes dominant), meaning females and males are equally likely to be affected. At present, there is no approved treatment for any genetic subtype; however, several therapies are under development, and in some cases, in clinical trials. These include both gene transfer therapies and other treatment modalities. In many cases, treatments under development will be specific to one or a few LGMD subtypes. While all genetic types of LGMD together have a similar incidence to more well-known types of muscular dystrophy, like Duchenne Muscular Dystrophy, the genetic heterogeneity of LGMD makes diagnosis and development of treatments challenging.

Overview: The virtual FDA Listening Session on Limb Girdle Muscular Dystrophies was held on October 20, 2020. This was a patient-led listening session organized by a group of advocacy organizations focused on various aspects and genetic subtypes of LGMD. Fifteen presenters, all patients or family members representing twelve LGMD subtypes, gave presentations in a webinar format which included personal narratives, slide presentations, and videos.

Major points raised by presenters living with LGMD:

- There are no treatments currently available for any LGMD subtype and it is urgent that we see treatments occur quickly and safely.
- Many treatments currently being researched or tested would only be applicable to one subtype of LGMD, complicating drug development.
- People with LGMDs often require many years to be correctly diagnosed.
- LGMDs are progressive, with major impacts on activities of daily living, ability to work and achieve independence, and personal and family life.
- LGMDs have a lot of common features which is why they are grouped together under the umbrella term. While LGMDs are different at a genetic level and vary in age of onset, patients with different subtypes often have similar loss of physical abilities.
- Most LGMDs cause respiratory weakness, which is a major cause of death in LGMD patients.
- People with LGMD often need a great deal of assistive equipment to function.
- Even within the same LGMD subtype, and the same family, age of onset and rate of progression can vary significantly.

- Some (but not all) subtypes have heart involvement, also a major risk to life.
- While patients would love for a future treatment to allow them to regain lost abilities, slowing or stopping further progression would be a meaningful benefit.
- The heterogeneous nature of LGMDs creates a lot of unique challenges for clinical trials — the patient community finds this very frustrating and wants to see things develop faster.
- Some individuals expressed concern that a rare disease has difficulty finding enough patients for a clinical trial; thus, placebo-controlled groups could be an insurmountable task.
- Most clinical trial readouts for muscular dystrophies are based on walking, which excludes a large proportion of LGMD patients from trials.
- Outcome measures within a clinical trial for a slowly progressing disease need to be sensitive to capture slight improvements.
- Some of the LGMD patients are dying while waiting for treatments to be approved: when appropriate, accelerated approval needs to be given and we need to see endpoints based on protein expression or another agreed upon measure.

Organizers

The LGMD Listening Session was planned and organized by a consortium of advocacy organizations, focused either on raising awareness or assisting patients living with LGMD and related neuromuscular diseases, or on achieving clinical trial readiness and developing treatments for particular genetic subtypes of LGMD.

- The Speak Foundation (uniting all forms of LGMD)
- Coalition to Cure Calpain-3 (focused on LGMD2A/R1)
- Jain Foundation (focused of LGMD2B/R2)
- Team Titin (Focused on LGMD2J/R10)
- Kurt+Peter Foundation (focused on LGMD2C/R5)
- LGMD Awareness Foundation
- CureLGMD2i Foundation
- Beyond Labels and Limitations
- Breathe with MD
- Camron's Cure (focused on LGMD2S/R18)
- LGMD2L Foundation
- LGMD1D/D1 DNAB6 Foundation

FDA Offices Represented (16 offices/divisions):

Office of the Commissioner (OC):

Patient Affairs Staff (organizer)
Office of Clinical Policy & Programs
Office of Combination Products
Office of Orphan Products Development
Office of Pediatric Therapeutics

Center for Biologics Evaluation and Research (CBER)
- Office of the Director
- Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/ Program Surveillance Branch
- Office of Tissues and Advanced Therapies, Division of Clinical Evaluation and Pharmacology/Toxicology/General Medicine Branch II
- Office of Tissues and Advanced Therapies

Center for Drug Evaluation and Research (CDER)
- Office of the Center Director
- Office of Translational Sciences/Office of Biostatistics/ Division of Biometrics I
- Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine / Division of Rare Diseases and Medical Genetics (DRDMG)
- Office of New Drugs/Office of Neurology/Division of Neurology I
- Office of New Drugs/Office of Neurology/Division of Neurology III
- Office of New Drugs/Office of Neurology

Center for Devices and Radiological Health (CDRH)
- Office of Strategic Partnerships and Technology Innovation/ Division of All Hazards Response, Science and Strategic Partnerships

Non-FDA Organizations (1):
- Reagan Udall Foundation for the FDA

Patients Represented

Fifteen presenters participated in the Listening Session. Of these, eleven are individuals living with LGMD, while the remainder are parents of affected children or adolescents. Patients are not identified by name in the synopsis but are referred to as presenters for anonymity. Collectively the presenters represent twelve genetic subtypes of LGMD:

- LGMD1D/D1 DNAJB6-related
- LGMD2A/R1 Calpain-3-related
- LGMD2B/R2 Dysferlin-related
- LGMD2C/R5 gamma-Sarcoglycan-related
- LGMD2D/R3 alpha-Sarcoglycan-related
- LGMD2E/R4 beta-Sarcoglycan-related
- LGMD2G/R7 TCAP-related
- LGMD2I/R9 FKRP-related
- LGMD2J/R10 Titin-related
- LGMD2L/R12 Anoctamin-5-related
- LGMD2S/R18 TRAPPC11-related
- Collagen VI myopathy/LGMDR22 Collagen VI-related

Note: Subtypes are specified using both the old nomenclature (number denoting the inheritance pattern followed by a letter denoting the specific subtype) and the recently revised nomenclature (letter denoting the inheritance pattern followed by a number denoting the specific subtype and the name or symbol of the gene involved).

Disclaimer

Discussions in FDA Rare Disease Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects the aforementioned partner organizations' account of the perspectives of patients and caregivers who participated in the LGMD Patient-led Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of LGMD, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire LGMD patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.

Financial Disclosures

Five participants made disclosure statements of financial relationships with drug developers. None of the participants received compensation from drug developers for their participation in the Listening Session.

Synopsis of Listening Session

FDA Opening Remarks

- Susan Chittooran, MSW (Patient Affairs Staff, Office of the Commissioner, FDA)
    - Welcome
    - Thanks for participation
    - Purpose and procedures of Patient Listening Session

Introduction

- Presenter 1 (female, 47) - lives with LGMD2I/R9 FKRP-related
    - Expression of gratitude to the FDA
    - Personal story shared from Presenter 1
        - Her age of onset - 6 years old
        - Symptoms began with repeated episodes of rhabdomyolysis after exertion
        - Initial diagnosis of Muscular Dystrophy with specific diagnosis of LGMD 2i years later
    - Serious nature of disease - relentless in its destruction and can be fatal
    - There are no FDA-approved treatments at this time
        - Request made for quick, safe clinical trials and treatments
    - 30+ subtypes of LGMD
        - Different yet sharing many characteristics
    - Thanks to all participating
- Presenter 2 (male, 57) - lives with LGMD2B/R2 Dysferlin-related
    - Personal story shared from Presenter 2
        - Age of onset - 18 years old
        - He had a healthy, athletic childhood and adolescence-typical of LGMD2B/R2
        - He lost the ability to walk 20 years ago
        - Today, he needs assistance for simple tasks

- LGMDs are 30+ diseases known as “subtypes”
  - All LGMDs are progressive diseases without treatments

Impact of LGMDs in Adulthood: Independence, Careers, Family Life

- Presenter 3 (male, 43) - lives with LGMD2A/R1 Calpain-3-related
  - His age of onset - 18 years old; “I felt my life was over” when diagnosed
  - Hope - a man in his sixties told him, “In your lifetime, there will be a treatment.”
  - He has lost all independent ability, except one: ability to sit to stand
    - Video of presenter - showing the extreme difficulty of sitting to standing
    - Takes about 2.5 minutes to stand
    - Takes all of his energy
    - Explained that if he loses this ability, he will no longer be able to be left alone at home, get out of bed, get up from his desk, or toilet
  - The hope he felt at 25 years is “diminishing.”
    - “If there was a treatment, it would give me more time to maintain this ability.”
  - “My hope is to reverse this disease.”
- Presenter 4 (female, 30) - lives with LGMD2J/R10 Titin-related
  - Her age of onset - 18 years old
  - LGMD2J is rare and hard to diagnose
    - Diagnosed after 6 yrs of testing (muscle and genetic)
    - Felt hopeless for a cure because of rare nature
  - Challenges and losses
    - She dropped out of college due to difficulty walking to class
    - Gave up independent living and job she enjoyed in CA due to rapid decline in strength, balance, and overall ability
    - Single mother
      - Became non-ambulatory during pregnancy and never regained strength
      - Requires help from mom and caregiver for physical needs and assisting with her daughter (unable to lift her due to arm weakness)
    - Insurance denial of power wheelchair
      - Makes use of mobility scooter paid for out-of-pocket, but can only use it outside of home
      - Inside the home she is limited by relying on someone to push her in a manual chair
  - Video shows morning routine and a typical day in her life
    - Getting out of bed and transferring into wheelchair with assistance

Impacts of LGMDs on Families with Affected Children: Quality of Life in Childhood and Adolescence

- Presenter 5 – this is a mother of two daughters living with LGMD2E/R4 Beta-sarcoglycan-related

- She shares a video of her daughters – a personal story and their daily life with two affected daughters
- Daughter 1
  - Her age of onset- 8 years old
  - Began with falls, trouble with stairs and getting in/out of car
  - Daughter uses a wheelchair full-time
  - Unable to do basic, everyday tasks (e.g. washing hair, dressing) without assistance
  - Requires a nurse with her throughout the day
- Daughter 2
  - Less affected, but recently started making use of wheelchair as well
  - Difficulty with left hip - walks with limp
- Greatest challenges
  - Watching her daughters struggle is heartbreaking
  - Points out that daughters have same disease but different rates of progression
  - Uncertainty and unpredictability of disease is especially hard
  - Heart is commonly affected with 2E patients - the "most disturbing thing"
- Disease variability - two children with the same subtype can present very differently
- Encouraged by clinical trials and hopes for treatment

- Presenter 6 – This is a mother of a daughter living with LGMD2I/R9 FKRP-related
  - Shows video of her daughter
    - Video shows daughter has difficulty getting up from floor and has marked weakness
    - Started physical therapy at 2 years old
    - Diagnosed in 2010
    - Progression - from active child involved in sports to more sedentary activities now
    - Current challenges for her teenage daughter with LGMD 2I/R9 FKRP-related
      - Frequently falls
      - Cannot climb stairs
      - Struggles to get up from floor; needs a stable, sturdy item to lean and push against
      - Limiting fluids due to difficulty ambulating to toilet
      - Recent surgery to address "toe walking" and has to wear casts
      - Will likely require spinal fusion due to muscle weakness/scoliosis
      - Missing out/being left behind
    - Hopes - "With treatment available, these dreams will be a reality"
      - Independence/more active
      - Dress herself
      - Ride a bike

        - Swim in ocean
        - Daughter can now work in the medical field which is her dream job, which is physically demanding
- Presenter 7 - mother of a son living with LGMD2S/R18 TRAPPC11-related
    - LGMD2S is very rare
    - Mother shares about her affected son
        - Physical and mental limitations
            - Loves cars, but cannot get license
            - Struggling to find the right job - cannot be on feet too long, but desk or computer jobs are above his cognitive ability
            - Family loves outdoors, but getting harder for him
            - Getting progressively weaker - heartbreaking to see him fall
    - Hopeful for treatment
- Presenter 8 - father of two sons living with LGMD2C/R5 Gamma-sarcoglycan-related
    - Variable course of disease among two boys with same mutation/diagnosis
    - Son 1
        - Active, involved in sports when younger
        - Was not obvious he had limitations
        - Faster progression
        - Some ambulation, but uses wheelchair
        - Struggles to get up from floor, holding a glass, lift heavy objects, roll over in bed
    - Son 2
        - Could not do sports when younger due to limitations
        - Mild progression
        - Still ambulatory now
    - Long-term health monitoring and actions are needed to check cardiac and pulmonary function, and maintain flexibility
    - Priorities
        - See damaged Gamma-sarcoglycan gene replaced - hope to slow disease progression
        - Convey tolerance of risks for potential treatment because of rapid decline
        - Access to treatment for non-ambulatory patients
        - Therapies to rebuild muscle

LGMD Context – Genetic Subtypes, Symptoms, Incidence

- Presenter 9 - (male, 41) LGMD genetics researcher and a patient living with LGMD2G/R7 TCAP-related
    - Age of onset - 19 years old
    - Synopsis of his work - Assistant Professor of Genetics at Yale University researching rare genetic diseases like LGMDs
    - What are LGMDs?

        - Group of diseases causing progressive weakness in hip, shoulder, proximal muscles
        - Originally a "catch all term" to distinguish from other more common types of Muscular Dystrophy
        - Genetically heterogeneous
        - ~30 LGMD genes known
    - Relatively Common LGMD Subtypes (with estimated US cases and typical onset)
        - LGMD2A, 2B, 2D, 2I- some of most common
        - European patient-centric data
            - Had to wait over 10 years to get diagnosed
            - His form, LGMD2G, is common in East Asia
            - Don't forget non-Europeans in research
    - Cardiac Involvement
        - LGMD can affect cardiac as well as skeletal muscle
        - Cardiologists should continually monitor heart function - suggested regular heart ultrasounds
    - Mental Health
        - Erodes sense of worth, isolating, and companionship is hard
    - Challenges of Therapy Development
        - Currently, no approved therapy for LGMDs
        - Challenges of genetic diagnosis

Impact of LGMDs on Activities of Daily Living and Adaptive Equipment Needs

- Patients with background in Rehabilitation Medicine
    - Presenter 10 (female, 33) - MD (physiatrist) and patient living with LGMD2B/R2 Dysferlin
        - She shares her personal story
            - Age of onset - 17 years old
            - Full-time wheelchair user
            - Hope - to remain stable in my strength at minimum or improve overall mobility
    - Presenter 11 (female, 59) - Worked as Occupational Therapist and patient living with LGMD2A/R1 Calpain 3-related
        - She shares her personal story
            - Age of onset - 5 years old
            - Diagnosed at 9 years old
            - Full-time wheelchair user since age 30
            - Hope - to regain some fine motor skill in hands and improve pulmonary function to not require ventilation
- LGMDs affect Activities of Daily Living (ADLs) - equipment becomes a necessity
    - ADLs include bathing, dressing, mobility, eating, toiletry, self-care, meal prep, and eating
    - Bed mobility
        - Discussed how there aren't any "Wake-up & Go" options with LGMD

        - Video - challenging process for Presenter 10 to get out of bed every morning using an adjustable frame bed
    - Bathing/Toileting
        - Individual has a loss of independence and dignity
        - Based on limited schedule of when others are available
        - Getting ready with assistance takes a long time
            - Takes 2 hours with assistance of husband every day
        - Aids - raised toilet seat, rolling shower, commode chair, bathtub lift
    - Dressing
        - Increasing difficulty as one loses upper extremity and trunk strength
        - Buttons and zippers challenging due to muscle weakness
        - Aids - button hook, zipper pull, reachers, dressing sticks, sock aid
    - Self-Care
        - Upper extremity weakness affects tasks such as brushing teeth and hair
        - Video - shows Presenter 11 moving head to brush teeth and inability to lift hands
        - Aids - long-handled brush and custom tool to put on glasses
    - Meal prep and eating
        - Upper extremity weakness affects ability to cut and eat food independently, as well as cook and prep food
        - Video - Presenter 11 eating with adaptive utensil
        - Aids - scoop plates, straws, jar openers
- Hope to at least stop or slow down unrelenting disease progression with minimal to no side effects

Adult-Onset LGMDs

- LGMDs do not always have childhood or adolescent onset
- Presenter 12 (male, 61) - lives with LGMD2L/R12 ANO5-related
    - Personal story
        - Active in 30-40s
        - Age of onset - 47 years old; 5 years before diagnosis
        - Now at 61, uses cane to walk and leg braces to prevent hyperextension, stairs and rising from low chairs are difficult to impossible
        - Has had 5 biopsies; involved in 3 different studies
    - Wide-range onset and level of progression for LGMD2L
        - 4 of 7 siblings have this diagnosis - some have no symptoms, while he has most advanced progression
        - Wide variability in terms of muscle pain, rate of progression, and genetic differences
            - 2 or 3 dozen mutations within subtype
    - Desired outcome
        - Maintain current muscle strength and, if possible, improve
        - Slow progression
        - Access to treatments

- Presenter 13 (male, 63) - lives with LGMD1D/D1 DNAJB6-related
    - Autosomal dominant subtype
        - Slower progression compared to recessive
        - Less common than recessive
        - May have cardiac involvement
    - Personal story
        - Inherited from father
        - "I've been slow all my life"
        - Walks with cane
        - Still preserved upper body strength
        - Wife passed away in 2017 - since then, physical adaptation and living independently is "approaching a full-time job"
        - Currently a practicing pulmonologist in CA - will need to give up working in next 5 years due to increasing weakness

Respiratory Impact and Risk in LGMDs

- Presenter 14 (female, 45) - lives with Collagen VI Congenital Myopathy/LGMDR22 Collagen VI-related
    - Respiratory involvement
        - Many are unaware of their respiratory weakness
        - Under ventilation during sleep can begin while ambulatory and leads to gradual buildup of CO_2 retention that is undetected
        - Cold or chest infection can escalate to pneumonia
        - Risk of respiratory failure can result in death
    - Personal story
        - Onset - 18 months
        - Can still walk short distances inside home, but with difficulty and safety issues
        - Takes long to complete ADLs
        - Drives adapted, wheelchair-accessible van
        - Works reduced hours
        - Forced Vital Capacity (FVC) is 36% of predicted
        - Uses non-invasive ventilation with portable ventilator (mouthpiece vent as needed in day and nasal ventilation for sleep)
        - Uses insufflator/exsufflator 3-4x a day to stretch muscles and remove mucus/prevent pneumonia when sick
    - Sister "Cheryl's story"
        - Vibrant until she was in sudden respiratory failure after being treated with oxygen without ventilation
        - The oxygen without ventilation made the CO_2 increase
        - Lost her in less than 9 days
    - Desired treatment - would slow or stop progression or make meaningful improvements in pulmonary function like Forced Vital Capacity and Peak Cough Flow.

- Presenter 15 (male, 57) - lives with LGMD2D/R3 Alpha-sarcoglycan-related
    - Personal story
        - First person to ever receive gene therapy for any Muscular Dystrophy - Dr. Jerry Mendell, Nationwide Children's Hospital, Ohio
            - Experienced no side effects, started producing gene
            - Accepted unknown risks
            - Hoped would last a lifetime, but was happy if only temporary benefit
            - Two weeks later - an unfortunate event when patient in a different trial died, which stopped all gene therapy for 5 years
        - In a wheelchair since 2004
        - Stopped working 2012
        - Cannot lift arms, drive, dress, or bathe self
            - If stronger, his wife could work outside of the house and wouldn't have to help with these things
            - Driving again would make big difference
        - Requires large amount of equipment needed just to leave the house - ramp, lift, bipap, shower chair, etc.
        - Desires "small things" - roll over in bed, slap a mosquito, wave to a friend
        - 5 of 7 siblings have LGMD2D and 2 nieces have 2I
            - Lost two sisters to respiratory failure (a "terrible death") and one sister has very poor lung capacity (32%)
    - Patient asks for:
        - Outcome measures to be changed
            - 50% of people with this disease being excluded
            - Proposes using heart and diaphragm muscle improvement as another target
        - Approval of treatment with only 6 patients per trial and not require the typical 12
            - If Phase 1 and 2 show safety and clinical benefit, approve with just 6 patients
        - Plan for "redosing" without risk
    - Believer in gene therapy - "We can make a difference in people's lives."
        - "Even if patients are not walking again, but show an improved quality of life (QOL), that is good enough."
        - Trials are needed soon, as patients are dying while they wait
- Presenter 1 (female, 47) - lives with LGMD2I/R9 FKRP-related
    - "Success" in drug development is seen differently by patients
        - Patients value and hope for:
            - Slowing or stabilization in progression of the disease
            - Breathe longer and better heart function for longer
            - Improved QOL
    - Most LGMDs progress slower than Duchenne, so outcome measures need to be more sensitive - slight improvements are hard to note and assess

- Call for patient reported outcome measures
- Treatments are needed for a wider range of patients - more inclusive drug treatment process for larger proportion of patients who are more progressed
- Some forms of LGMD are ultra-rare, meaning it would be near impossible to have control groups with some subtypes
    - Expecting natural history studies for every subtype is not effective - wants to see them combined and outcome measures shared across subtypes
- Need accelerated approval for treatments
- Call for different "end points" - look at biomarkers for protein expression
    - More patients could be included this way and therefore more patients can access treatment

Closing Remarks from Patients

- Thank you to FDA
- Future plans for patient advocacy as a community - participate in Patient-Focused Drug Development sessions
- Patient community wants to play an active role in drug development

Open Discussion with FDA

- FDA: How do you accommodate the broad diversity of this disease, in a clinical trial or multiple trials?
    - Patients: Most treatments (including all gene therapies) will only apply to one subtype, so for that reason, you would usually need the trial to be subtype-specific. However, some of the outcome measures do seem to transfer across subtypes. For instance, an outcome measure (secondary) used in the 2E gene therapy trial was actually developed for 2B and adapted from DMD. 2E gene therapy is already well into clinical trial right now, but it is a fairly rare subtype. Some therapies may be able to be tested across subtypes (i.e., new steroids).

      For example, recently, Northwestern ran a cross subtype trial with once-weekly-dosed prednisone [this is an off-label use of an approved drug and therefore not directly overseen by FDA]. There are currently several subtypes with prospective treatments either in clinical trials or in preclinical testing.