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ReachMD

www.reachmd.com

info@reachmd.com

(866) 423-7849

LGMD in Focus: Early Diagnosis, Precision Subtyping, and Targeted Therapies

Announcer:

Welcome to CME on ReachMD. This activity, titled *LGMD in Focus: Early Diagnosis, Precision Subtyping, and Targeted Therapies*, is provided by The France Foundation. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Batley:

Hello, welcome to *LGMD in Focus*, where we'll be discussing the early diagnosis, precision subtyping, and targeted therapies for limb girdle muscular dystrophy.

Hello, I'm Kaitlin Batley. I'm a pediatric neuromuscular neurologist at UT Southwestern in Dallas, Texas.

Dr. Karachunski:

Hello, I'm Peter Karachunski, and I'm a pediatric neuromuscular neurologist at the University of Minnesota.

Dr. Batley:

So this educational activity was provided by support from BridgeBio, and today we'll be discussing limb girdle muscular dystrophy and going through its subtypes and novel approaches for therapeutics.

So today we'll begin with a case study and discuss the genetic classifications of different limb girdle muscular dystrophies, as well as the latest in clinical trial data for emerging therapies.

So let's begin by discussing how we improve the early diagnosis of limb girdle muscular dystrophy. Limb girdle muscular dystrophies are a heterogeneous group of muscle disorders that typically begin with proximal muscle weakness that begin in a limb girdle distribution, and this involves typically the hip girdles and the shoulder girdles, as you can see here outlined in red in the diagram, and it can lead to severe disability and even early mortality. And it can be caused by one of numerous different genes, over 30 of which have been identified currently.

The majority of our limb girdle muscular dystrophies are associated with significantly increased creatine kinase levels in the blood, and on muscle biopsy, we typically see muscle degenerative changes. Each LGMD is by itself very rare.

Collectively, they are still considered a rare disease with a prevalence of about 1.6 per 100,000.

LGMD subtypes have been identified to be caused by over 30 different genes. These can be divided into autosomal dominant and autosomal recessive conditions, which we'll talk about in a bit more detail later. You'll see here are two different classifications of these disorders. The first starting with the letter D, and then followed by a number, and then in parentheses you'll see it kind of the opposite, starting with a number 1 and then a letter, and similarly with recessive, starting with R and a number and then a number and letter in parentheses. And that's because this classification system did change in 2018, and now instead of using the letters to indicate the subtype, we use numbers. And so the D stands for dominant, recessive is indicated by letter R, and then the numbers actually indicate the gene. And you can see here on the diagram that these different genes are involved in different facets of muscle pathophysiology, extending from the extracellular matrix all the way down through the nucleus of the cell.

Here is the list of the different genes that have been identified to be implicated in limb girdle muscular dystrophies, and the LGMD-D genes are listed in the first column, and LGMD-R in the second. Then you'll see over in the third column that there are a host of different conditions that can sometimes present with similar symptoms and can be seen to also have that same limb girdle distribution, but that are technically classified separately from the limb girdles as a whole.

And as we talk about the pathophysiology of limb girdle muscular dystrophy, this is also a very heterogeneous etiology. So some of the different LGMDs can lead to defects in the dystrophin glycoprotein complex. Others, defects in nuclear function or impaired signal transduction, as well as loss of sarcolemmal integrity, errors in glycosylation, and impaired vesicle and molecular trafficking. And each of these different categories are caused by different genes, and you'll see the different limb girdles identified in each of the boxes.

And as we review the genetic inheritance of limb girdle muscular dystrophy, it's important to note that nearly all—about 90%—are caused by autosomal recessive conditions, and so this typically means that there are two unaffected carrier parents that then, in reproduction, each pass on an abnormal variant in the particular gene to then cause their son or daughter to receive two copies of this gene that are not functioning correctly and thereby have the condition, and this does lead to about a 25% chance of recurrence risk in each pregnancy. Then, in a smaller number of cases, the condition can be inherited in an autosomal dominant manner, whereby an affected parent passes it directly down to an affected child, typically leading to a 50% inheritance risk.

And as we have learned more about the different limb girdle muscular dystrophies and identified the different genetic etiologies, we have learned a little bit more about the prevalence and which ones tend to be the most common. These can include calpain, dysferlin, FKRP, ANO5, and the sarcoglycans, but it can be really challenging to actually understand the true prevalence, and this is due to many different causes. One of which is underdiagnosis and underrecognition of these conditions, especially when they present in their more mild forms. We also know that our epidemiologic data is not equivalent, and that there can be different areas that tend to see these conditions more prominently because of things like founder effects.

And in general, limb girdle muscular dystrophies are a very wide spectrum. We typically define them by the age of onset and the achievement of ambulatory status, and classify LGMDs as beginning after about 2 years of age, with some subtypes even having diagnosis and onset of symptoms that begins in adulthood. And we try to kind of distinguish this from the similar conditions that can be caused sometimes even by the same gene, but that begin with symptoms that were perhaps right at birth or later in infancy, and these individuals tend to have a more severe phenotype, and we classify those as congenital myopathies or muscular dystrophies.

We also know that the muscle weakness in the progression of disease occurs at different rates, and this can depend on the specific gene and the specific variant in that gene, as well as epigenetic modifiers and things that we probably don't fully understand yet. And because of this, the genotype doesn't always match the phenotype.

Because of the rarity of these conditions and the difficulty with diagnosis, there are still many unmet needs in limb girdle muscular dystrophy, and one of these things is just that misdiagnoses are very common. There can be a wide variety of symptomatology, and because of this, we sometimes don't always get to the correct diagnostic point. And so it's important to remember that genetic testing is something that progresses over time, and that with the advent of improvements in our ability to identify these genes to find things like intronic variants and more rare and complicated genetic diagnoses, that these are things that need to be reevaluated with time. Even if you have a patient who previously had genetic testing, it is something that sometimes needs to be redone.

We also know that even when we identify the correct gene to cause a particular LGMD, that because these are rare diseases, we don't always have the very comprehensive natural history studies done that can help us understand what these disorders truly look like over time, as well as identify sensitive biomarkers and clinical outcome measures that we can use to then work through interventional trials and determine the potential for improvements with outcomes.

And because of this, and where we're at in science right now, we don't have any currently approved FDA therapies. Although we will talk at the end about some ongoing clinical trials and some really exciting things that look to be coming down the pipeline.

So, red flags that should raise your suspicion for LGMD, of course, any family history of neuromuscular disease. A parent or other family member who maybe had an unexplained reason for using a wheelchair later in life, or who developed a cardiomyopathy, should always kind of raise the red flag for could this potentially be an LGMD? And this can look like lower extremity complaints, like a slow waddling gait, difficulty with climbing stairs or getting up off the ground, indicated by a positive Gower sign, things like difficulty with walking and running. Some patients will say that they were always kind of lagging behind their peers growing up and were always kind of in the slowest group, and that's because they had this subtle muscle weakness that wasn't quite identified.

Similarly, looking at the shoulder girdle, we can see things like difficulty carrying heavy objects, difficulty raising the arms above the head, or doing things like brushing your hair, which requires, you know, your arms to be up for a prolonged period of time, in trouble with

fine motor skills. Other red flags are things like elevated CK identified in the bloodstream, and this can sometimes first be indicated by kind of an elevation in what we typically call our liver function tests, or LFTs, but that we also know are a sign of muscle breakdown as well with AST and ALT. And so having this kind of transaminitis should always kind of prompt you to check for CK as well to see if these liver function tests could actually be elevated because of muscle breakdown. And then other things on the exam that can point towards a limb girdle muscular dystrophy are things like scapular winging because of shoulder girdle atrophy and weakness, as well as calf pseudohypertrophy or conversely, atrophy and contractures, particularly of the ankle joints.

Different LGMDs can also have some variances in their clinical presentation and in the organ systems that are involved. So, for instance, cardiac involvement can be seen in numerous different LGMDs. Respiratory involvement also is a fairly universal feature with more advanced stages of disease. Joint contractures are extremely common, as well as some LGMDs having distal muscle involvement predominantly in addition to the proximal muscle. And then, although biopsy is a little less common than it used to be, there could be specific biopsy features on muscle biopsy that indicate a particular LGMD. And then also understanding the background of a patient and maybe where their family is from can also point you towards different genes if there could be a founder effect in that area.

So potential complications with LGMDs are multisystemic, just like many other neuromuscular disorders. And we know that with progressive muscle weakness, we can see things like frequent falls, loss of the ability to independently ambulate, and the need for mobility aids and wheelchairs. And then later on, difficulties even with things like transferring yourself, and then requiring assistance with ADLs in many cases. There can also be musculoskeletal and orthopedic complications that can develop as a consequence of weakness, such as joint contractures and scoliosis, and this can lead to chronic pain as well as having low bone density from immobility and lack of weight-bearing activities, which can increase risk for fractures, which can also be an important contributor to pain as well.

We know that cardiac disease can be very common, and this can include both cardiac muscle disease and cardiomyopathy, as well as aberrant rhythms and arrhythmia, and so there is an increased risk for things like heart failure and sudden cardiac death. And similarly to other neuromuscular disorders, respiratory complications can occur, which can lead to initially in early stages sleep-related hypoventilation, and so sometimes the need for nocturnal positive pressure ventilation, as well as later on, more significant restrictive lung disease, things like dysphagia can lead to increased risk for aspiration and recurrent infections and pneumonia as well.

So once you have an initial suspicion for limb girdle muscular dystrophy, the assessment can really vary from getting your answer right away with things like genetic testing to having to do a little bit more as far as the diagnostic odyssey. So our medical team should always be, you know, identifying family history, physical exam, pattern of weakness. And then oftentimes that will be what actually triggers us to send broad neuromuscular genetic testing, either through the use of a- a gene panel, many of which are sponsored and so can be obtained without cost to the patient. And if the answer is obtained in that way, then oftentimes other ancillary testing such as muscle biopsy, EMG, muscle MRI might not need to be done. But once we do identify the variant, things like cardiac testing and respiratory pulmonary testing is also very important, and that's kind of longitudinal follow-up that needs to be done throughout a patient's life.

So, looking at our clinical investigations, CK is a very common and easy test to obtain. It's done in nearly every laboratory and is probably the most cost-effective test, but it's also not specific to a particular LGMD or even a particular muscle disease. So this is something that patients are often identified to have an elevation in, and then that actually leads to their referral for more significant testing. And then similarly, like I mentioned, this alteration in what we typically call the liver function tests, or LFTs, but that are actually also a marker of skeletal muscle breakdown, can be kind of the first indication of an underlying LGMD, and oftentimes even in asymptomatic or presymptomatic patients, this can be what triggers them to find the diagnosis.

Many individuals will also have electromyography done, and this typically shows normal nerve conduction studies. And then the actual EMG portion can identify a myopathic pattern with short-duration, low-amplitude motor units, and sometimes there can be some spontaneous activity with significant muscle membrane irritability. And muscle MRI, which is not done universally, but is becoming a more prominent tool and has been used in some outcomes in clinical trials, can show fatty replacement in different characteristic muscle groups that can indicate one LGMD over another. And then muscle biopsy, of course, is more invasive and so not done in every case, but can be incredibly helpful, especially when we are trying to clarify a variant of uncertain significance that may have been identified on our genetic testing.

Now that we have talked about how to make the diagnosis in limb girdle muscular dystrophy, let's talk about why this is so important. We know that with early diagnosis, we are able to perform preventative surveillance to anticipate and identify conditions that may occur in other organ systems, such as cardiomyopathy, before they become a significant problem. This can also help us with family counseling and planning to identify either other affected individuals or help our families make decisions about their future reproductive plans. And this can also help our patients access trials and potential for emerging therapies more expeditiously.

And when we don't make these diagnoses in a timely fashion, and the diagnosis is delayed, we oftentimes miss the opportunity to

provide supportive, proactive cardiac and respiratory care, which can then lead to preventable complications, things like increased frequency of aspiration pneumonias, cardiomyopathy that is leading to things like arrhythmias that aren't identified and can really significantly increase morbidity and mortality.

So, as we talk about how to make this diagnosis, I think we need to focus on the availability of next-generation sequencing panels for genetic testing. So, once a patient is determined to either have the characteristic pattern of weakness or a particular inheritance pattern in their family for neuromuscular disease, or even the identification of an asymptomatic elevated CK, we need to remember that there are these very cost-effective, oftentimes sponsored panels that are available to perform genetic testing. And oftentimes, if our answer is found here, we are able to stop our diagnostic odyssey and confirm the diagnosis and move forward with a treatment path.

However, we do still have the ability to perform things like nerve conduction studies and EMG, as well as muscle biopsy or muscle MRI, if we then are faced with things like variants of uncertain significance in our genetic testing. And then if our additional tests, you know, remain unclear, then we also should be kind of constantly going back to reevaluate the diagnosis and look for alternate etiologies.

So let's work this through with a case study of our hypothetical patient, Jonah. So this is an 18-year-old young man who presents with several years of exercise intolerance, muscle pain, and slowly progressive weakness. He's noticed that he's had difficulty climbing upstairs. He's always kind of had trouble keeping up with his peers at school, and now he's started falling. And when he gets up from the ground after falling, it's become more challenging; sometimes he needs to have someone help him. He denies any ptosis, dysphagia, diplopia. And so as you're hearing his history, we're seeing an exam that's pertinent for weakness of the hip flexors as well as shoulder abductors, a positive Gower sign, and a waddling gait, and he's noted to have calf pseudohypertrophy and scapular winging.

So important takeaways from this section is the crucial early diagnosis. So we know that patients with progressive proximal weakness, scapular winging, Gower sign, this transaminitis or unexplained hyperCKemia, should always be tested for genetic muscle diseases such as limb girdle muscular dystrophies, and that we should consider this as an underlying etiology even before the progression of clinical weakness, and sometimes this unexplained CK elevation can be the first clue. And when we do see an elevated AST and ALT, although it oftentimes is attributed to liver disease, checking a CK is extremely important. Our history, exam, genetic testing, CK level, and then the potential for other testing like EMG, muscle MRI, and biopsy are core tools when we're considering a limb girdle muscular dystrophy. And then once we do have the diagnosis confirmed, remembering the importance of our multisystemic care, things like cardiac and pulmonary management.

Dr. Karachunski:

Okay. Now, once we've discussed the overview and diagnostic algorithm for limb girdle muscular dystrophy, I'd like to focus specifically on genetic analysis and how we can interpret the genetic test in this condition.

So let's go back to our case study, and the workup showed that the creatine kinase elevation was rather significant at 8,000. There is normal initial cardiology and respiratory evaluation. Muscle MRI shows fatty replacement of the muscles in the posterior thigh, which is highly suggestive of limb girdle muscular dystrophy as a diagnostic possibility. So the next step was to send for a genetic analysis, and this result came back with a pathogenic variant, which is rather common in this condition that is consistent with the diagnosis of fukutin-related protein related limb girdle muscular dystrophy.

So the question is, why do we care about the genetic test, and why do we need to know the specific diagnosis? And there are a variety of reasons for that. One is that knowing the specific genetic diagnosis of limb girdle muscular dystrophy, we can go back to what we know about this particular form of limb girdle muscular dystrophy and predict its natural history, potentially complication that would allow us to provide targeted surveillance and management. It would be important for family counseling and providing them with the relevant information about family planning and other family members who are at risk of having the same condition. It also allows us to state and genotype-guided treatment when it is available, and prognostication of the disorder can be helpful for some people as they plan their future life, family building, and so forth. It's also important for our research community to classify these patients and allow build the registries and potential participants in clinical studies and clinical trials going forward in development of novel and disease-modifying treatments.

Currently, the genetic test is a gold standard for diagnosis, and there are several approaches right now. This can be done utilizing single or multigene panel testing, deletion or duplication analysis, whole exome testing, and genome testing. So, in general, if you see a patient without a family history and a non-genetic course, we would go directly to multigene panel testing that utilizes next-generation sequencing technology and allows to identify potential variants in the genes that are known to cause limb girdle muscular dystrophies. Deletion and duplication analysis commonly is associated with this next-generation sequencing, and less commonly used right now as more sophisticated genetic testing are available to us, such as whole exome testing and genome testing.

Whole exome testing would be helpful in the case if there is, especially family history of the disease and first-line genetic test such as a

multigene panel was negative, so that there is a potential for identifying novel genetic causes or some other variants that potentially can be responsible for the genetic cause of this form of limb girdle muscular dystrophy.

Genome testing is even more sensitive, and it also encompasses intronic sequences that now more frequently recognized as potential cause of the genetic disorders.

So, how do we choose what the genetic test is best for the patient? As I mentioned before, single-gene testing is useful when there is a known familial variant and clear phenotype associated with the disorder, and can be tested in both symptomatic and a asymptomatic patient. However, in general, we do discourage testing asymptomatic patient unless there is an effective disease-modifying treatment available.

Multigene panel is the first line and it's very sensitive and useful and the sensitivity is going up as patient has a recognizable pattern of involvement and elevated CK, and some possibly other positive ancillary testing such as MRI of the muscles and abnormal EMG.

Deletion and duplication analysis useful for copy number variants and missed by sequencing would be an additional testing to the first-line, a multigene panel, which can be easily replaced by whole exome sequencing if feasible. And this, as I mentioned before, can be useful in those fairly apparent phenotypes but negative next-generation sequencing testing, similar to with the genome and sequencing, as it also is capable of showing structural changes and non-coding variants, and is useful also for conditions such as due to repeat disorders.

So, how do we interpret result of genetic panels? And as opposed to many other tests, it's not a black and white answer quite often. And there are different classifications of the variants. And the most clear one, which is called pathogenic, which is variant that causes the disease. And this classification is based on the sufficient evidence that this variant causes disease, and it was previously seen in other patients with the same condition. Likely pathogenic has a very good biological plausibility and some evidence supporting the disease, but may have somewhat lack in clinical evidence.

The next possibility is the variant of uncertain significance, and these variants create most of the challenges to make a diagnosis, as those variants usually rarely seen in population and have unclear biological plausibility to cause the disease. And those variants create the most challenges and unfortunately they are most common encountered during diagnostic testing. And then there are likely benign and benign that variants that are not associated with disease-causing phenotype and unlikely to be the cause of this particular presentation.

So the results can come in different flavors and combinations, and it can come with one pathogenic and one likely pathogenic variant if it's recessive, and then it can be most likely associated with explanation for the disease, and that's very helpful. And then it would be more likely associated with a dominant disorder if it's a single copy. However, it can present in a homozygous or heterozygous configuration, and it is important to demonstrate that these variants are in transposition, so that they are present on different alleles, and those variants likely to cause recessive form of limb girdle muscular dystrophy.

The other combination is one pathogenic and likely pathogenic variant, and just one allele, and but is associated with the recessive limb girdle muscular dystrophy, then it is highly suggestive that this individual is a carrier for this disease, but likely to be asymptomatic. However, some of the limb girdle muscular dystrophies can present as recessive and as dominant form due to the same gene variant. Quite often, those variants are recognized as likely to cause dominant or likely to cause recessive. So it's a matter of further analysis and the help of a genetic counselor to decide about significance of this finding.

And then of course challenges can be related that the pathogenic variants are found, but the presentation of the patient is not consistent with expected phenotype. It could be due to different time of onset or different pattern of presentation, and then this may or may not be an explanation for the patient presentation and further testing and clinical monitoring is required. As I mentioned before, variant of unknown significance is most challenging and would require further analysis and additional ancillary testing.

Negative panel does not entirely exclude inherited myopathy or even limb girdle muscular dystrophy, but would require additional evaluation with broader neuromuscular testing, ancillary testing, and also clinical monitoring.

So, role of genetic counselor is critical, and it is one of the core specialties in our neuromuscular clinics to support our patients and facilitate diagnostic process and help to interface with the family and patients in discussing the results, coordinating the testing, providing explanation about challenges in the diagnostic, and also counseling the family, discussing reproductive and family planning options, as well as potential risk for development of the condition for other family members.

In this section takeaways, I hope I was able to show you that genetic testing is considered the gold standard for diagnosing limb girdle muscular dystrophy. It's the most common. First genetic test employs a multigene panel, and the results from genetic tests can help guide treatment and management of patients with limb girdle muscular dystrophy. Genetic counselor is a critical team player in

evaluating a patient with suspected genetic cause of muscle condition and helps facilitate communication with patients and families and coordinate additional care.

Dr. Batley:

Now that we've discussed limb girdle muscular dystrophies as a whole and the importance of early diagnosis and how we make this diagnosis, let's talk about some of the latest clinical trial data and the upcoming emerging therapies.

So, in order to actually identify whether these therapies are making a difference in the lives of those with limb girdle muscular dystrophies and improving functional outcomes, one of the first most important steps is to obtain natural history information and a good understanding of what these disorders look like without treatment. And so, as of right now, there are about seven different natural history and observational studies that are going on, looking at the different limb girdle muscular dystrophies, looking at the genetic background and how that correlates to phenotype or symptomatic presentation, assessing motor parameters over time, looking at biomarkers in particular cardiac involvement, respiratory involvement, and are enrolling patients into these registries to follow them longitudinally. And there are a handful of different LGMD subtypes that are currently being investigated.

And concurrently with our new and emerging therapies, as well as the way that we are gathering evidence for what these disorders look like over time, we also need to keep our focus on the cornerstone of care, which is this multidisciplinary supportive management, and this involves numerous different specialists that are focusing on each organ system of the body. And these specialty care guidelines were initially published by the American Academy of Neurology over a decade ago, and then recently reaffirmed as well, and does involve an entire care team with members from cardiology, pulmonology, physical therapy, nutrition, orthopedics, and everyone to help optimize outcomes even without disease-modifying therapies.

So our goals throughout this time are to reduce muscle weakness and loss of function. And so in the future, I hope this will mean an actual disease-modifying therapy that aims to target the genetic cause of the different LGMDs. But in the meantime, we know that outcomes can be significantly improved with physical and occupational therapy, a focus on exercising and stretching, as well as mobility aids and orthotics. And this involves cardiac monitoring and proactive strategies to manage heart failure if it were to occur, or even some of our preventative heart failure strategies, monitoring for rhythm abnormalities, and sometimes this might lead to things like pacemaker implantation or ICD, cardiac transplantation, and advanced cardiac therapy with things like left ventricular assist devices, or LVADs as a bridge to transplant can be also utilized. Things like close cardiac and pulmonary monitoring with frequent PFTs, non-invasive ventilatory support, and airway clearance when needed, as well as optimizing nutrition through close communication with a dietitian if needed, modification of the diet to make things perhaps easier to swallow, or to optimize caloric intake. Working with a feeding or speech therapist to work on the actual swallow function if there is dysphagia or an increased risk for aspiration. And then sometimes this can also mean alternative methods of nutrition as well, such as gastrostomy tubes.

So, as we look towards potential therapies for the future, what would actually constitute a meaningful benefit for our patients with LGMD? So these therapies focus on the biologic basis of the particular LGMD and aim to make a change in the actual pathophysiology of the disorder. This then would hopefully lead to a functional change for the patient and then their perceived benefit in perhaps their strength or their energy level, make activities of daily living easier to do things like that that will bring real benefit to a patient's daily lives.

So the GRASP-LGMD Consortium is currently ongoing study of almost 200 patients across several different LGMD subtypes. The goal of finding which of these clinical outcome measures are reliable, which respond sensitively to change and progression of disease and could potentially be impacted by a disease-modifying therapy as well. And so, data from this can help inform clinical trials in the future.

And there are currently four different emerging therapies across the LGMD subtypes that we'll go through in a bit more detail, and you can see several of these are gene transfer therapies, and one is a small molecule therapy, and we are looking at three different LGMD subtypes as we review these therapies.

So before we start talking about the individual gene therapies under investigation, let's talk about this class of therapies as a whole. So these products are designed to utilize a DNA code for a particular missing DNA product, such as FKRP. And this actual transgene is then packaged into a viral shell or capsid, which can then be administered to the body, typically through IV in these cases. This then travels throughout the bloodstream to its different target cells. The viral vector attaches to the target cell and then releases the transgene, and then the body is actually able to express this protein, and then we can see the protein product being targeted throughout the body.

First, let's talk about bidridistrogene xeboparvovec, and this was evaluated in the EMERGENCE phase 3 study. This product uses the beta-sarcoglycan transgene, packages it inside of a viral vector, and this particular vector is the AAVrh74 viral vector. And this then is administered one time to a patient in this case greater than or equal to 4 years old, confirmed to have limb girdle muscular dystrophy due to beta-sarcoglycan, and this is given one time. And they tested both ambulatory and non-ambulatory individuals, and had clinical

follow-up over 60 months at this time period.

And the primary endpoint in this study was the mean change from baseline to day 60 in beta-sarcoglycan expression, and this was measured by percent positive fibers in immunofluorescent staining, and they did this in ambulatory individuals.

Secondary endpoints also looked at additional muscle biopsy details with beta-sarcoglycan expression in different modalities, as well as a change in CK level and safety throughout the process.

So the outcomes that were seen in this study did show a significant change from baseline in the expression of beta-sarcoglycan. And you can see here that ambulatory individuals had a 38.6 change from baseline, and non-ambulatory individuals had a 21.9% change from baseline. Overall safety was evaluated, and the safety was consistent with the kind of class effect of gene therapies. And the most common things seen were nausea, decreased appetite, and vomiting. And there was an incidence of acute liver injury that occurred in these patients, as is similar in other AAV gene therapy studies, but there were no treatment-related deaths or acute liver failure.

Next, let's talk about AB-1003, which is being evaluated in the phase 1/2 LION-CS101 trial. So this is similarly a gene therapy using an AAV viral vector, and this one is targeted towards LGMDR9 using an FKRP transgene. This study is earlier in its progress and is enrolling adult patients ages 18 to 65 and is evaluating different motor function outcomes. So far, we have some early safety readouts that have shown no serious adverse events through 52 weeks. There were again similar class side effects such as nausea and also headache seen as well as falls, and there were transient AST and ALT elevations that occurred in three patients, but were determined to be asymptomatic and without bilirubin changes that resolve to baseline after adjustment of concurrent corticosteroids.

Next, we'll talk about ATA-200 in the phase 1/2 ATA-003-GSAR trial. This is a single-center study that is enrolling children who are ages six to 13 years old, also utilizing an AAV gene therapy, which is carrying a gamma-sarcoglycan transgene given through a single IV injection. So, in the first two patients who were treated, we do have some outcomes that were seen, including a 90% expression of gamma-sarcoglycan in muscle fibers at 6 months, as well as a significant and sustained reduction in creatine kinase levels, and at 9 months post treatment, these two individuals were noted to have clinical benefits in their timed functional motor tests.

And the last therapy that we'll discuss is BBP-418, or ribitol, which has been evaluated in the FORTIFY phase 3 trial. So this is a therapy that is directed towards patients with LGMDR9. And in this particular trial, they enrolled individuals age 12 to 60 years old, and their key outcome measures were different motor function tests, such as the NSAD, as well as timed 10-meter walk test and 100-meter walk test. They also evaluated upper limb function with the PUL and pulmonary function, as well as biomarkers such as serum creatine kinase and the glycosylated alpha-dystroglycan levels.

So ribitol's mechanism of action acts by adding additional ribitol into the body to increase the substrate to allow glycosylation of alpha-dystroglycan. In patients with FKRP-related LGMD, this alpha-dystroglycan is extremely unstable and is unable to maintain muscle membrane integrity, and so by improving glycosylation, we're thereby strengthening muscle membrane integrity. So in this therapy, there was a 2:1 randomization of patients who received ribitol to those who received placebo, and then afterwards there was a crossover followed by an open-label extension.

So the outcomes of the use of ribitol in the FORTIFY study are seen here, with a significant decrease in the mean serum CK levels in those who were taking ribitol. So you can see in this graph on the left that we have a gray line that indicates the placebo patients, and you can see their CK falls in the 2000 range, which is fairly typical for an LGMD. And then the lines in the very bottom in red are those who do not have LGMD and who have kind of their normal CK level. And then you can see in the blue line are treated patients, whereby you can see that their CK started around the same range as the placebo, and then dropped precipitously by 3 months, and remained low and really approached the normal level for CK. And so you can see an 82% decrease in patients who were taking ribitol, which is statistically significant compared to placebo.

We also can see here a mean change in motor function tests, and the outcomes here can see that there was a significant change from baseline in those who were taking ribitol, with an increase in velocity of 0.14 meters per second compared to the placebo group, which actually had a decline in velocity, and so the actual difference was 0.27 meters per second, which is what was statistically significant as far as motor function outcomes over this 12-month time period as well.

So, of course, the study also evaluated safety and the most common treatment-related adverse event seen was diarrhea, seen in 40% of patients compared to placebo, which was about 50%. And this was all-grade 1/2. There were 5% of grade 3/4 adverse events. Nobody discontinued due to an adverse event, and there were no deaths or serious treatment-emergent adverse events.

So, as a whole, I think the important things to take away from these clinical trial outcomes are that there is significant progress being made in the future of treatments for LGMDs. We do know that these clinical trials are not available for all subtypes of LGMD, and that there is a significant space to improve this and expand to all of the different subtypes. Right now, there are no approved therapies for

LGMD, although, as you can see, some of these are approaching that with phase 3 trials. And so we are hopeful that there could be approved therapies in the future, and that these therapies truly could have the potential to slow the progression of disease for those with LGMD and significantly improve morbidity and mortality and quality of life for these patients. We are still, as we work through these clinical trials, working to understand what are the most important and sensitive markers of efficacy, as far as clinical benefit, and so these trials are underway with things like natural history studies as well.

So now let's take it back to Jonah's long-term care. So Jonah, our hypothetical patient, has established care in a multidisciplinary clinic. He's now seeing a neuromuscular neurologist, a pulmonologist, and a cardiologist regularly. He attends PT once a week and has started a daily stretching regimen with the nightly use of orthotics. He's eating a healthy diet, remaining hydrated. But of course, he is asking about what his possibilities are for disease-modifying therapies for the future, and wants to talk about enrolling in a clinical trial.

So as we prepare to make these kinds of decisions, the role of shared decision-making is really crucial. So of course, on our end, as the treating physicians confirming a patient's genotype, phenotype, their functional status, their cardiopulmonary health, these are all important in how we make our recommendations. And obviously, knowing genotype is crucial, which is brings us back to the beginning of why diagnosis is so important because this helps us know what studies to offer.

I think it's also our job to provide all potential options, and this could include, you know, our current standard level of care with supportive management. This could include referral to another site that might have, you know, a natural history study to offer, and even referral into a trial as well. And so, all of these options should be presented neutrally to help a patient make their decision.

We also do need to use language that's relevant to our patients to help to describe what their expectations could be for change in function, what safety looks like, and not just focus on things like biomarkers or things that are too science heavy, and also explain what this actually means for them in their lives.

And then also understanding our patients and getting to know them to understand what is most important to them. Everybody will weigh potential pros and cons of different therapies differently, and for some people, the burden of a clinical trial or the potential risks that go with taking a therapy that is under investigation might be not within their wishes, and that's absolutely appropriate. And so, understanding what's important to them can help us to make our decisions together. And then making a coordinated plan and making a plan for when we will check in again to reassess this. Maybe they say, you know, "a clinical trial for me, this is not a good time, but I'd love to talk about it again in 6 months" or vice versa. And then also, as a patient progresses in their disease and as their functional outcomes can change, this could mean, you know, differences in their care and differences in what they need to do. Also, you know it is our role to stay up to date with current therapies and current trials to be able to bring those to our patients when they do come about.

So, main takeaways from this section is that we do need to remember that our multidisciplinary supportive care is still crucial and key, and we need to focus on this method of kind of systematic whole body and whole person care, in order to help set our patients up for success and to optimize their health for when hopefully these new therapies do come into play, that we do need to focus on natural history data, especially for our more rare LGMDs that are perhaps not as well understood, and to always remember to be looking out for these new interventional clinical trials that are underway and coming to bring hope for new therapies for the future for our patients.

Dr. Karachunski:

Let me now summarize what we've covered during this talk. And key takeaway points here would be that limb girdle muscular dystrophy symptoms can be fairly non-specific, especially early in the course of the disease, and should be considered as a differential diagnosis for individuals with proximal muscle weakness, with or without hyperCKemia. Early recognition of limb girdle muscular dystrophy is crucial, as it is critical to provide proactive and preventive care for multi-systemic involvement, including cardiac and pulmonary, as well as potential for new therapies that hopefully coming soon. And genetic testing can be now performed in a very quick and cost-effective manner to identify individuals with potential limb girdle muscular dystrophy.

Announcer:

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