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Hello, my name is Eric Wallace. I'm a professor of medicine at the University of Alabama at Birmingham in the Division of Nephrology and the Department of Medicine. And today, we're going to talk about Fabry disease research highlights. This is our continuing education information, and you can see my disclosures there below. Fabry disease is a rare X-linked lysosomal disorder caused by mutations in the GLA gene.

This leads to a deficiency in alpha-galactosidase, which causes an increase in global triacyl ceramide and lyso-Gb3 to build up in cells and cause damage. Characteristically, this leads to the phenotype of acroparesthesia. So patients, sometimes, in classic males at the age of five, will start getting pains in their hands and feet. This typically progresses into adulthood and can be very, very severe. Some of these acroparesthesias or these pains can cause pain crises, specifically in extremes of temperature when the patient is sick.

It can also lead to proteinuria and kidney disease. This is because the lyso-Gb3 and GL3 actually build up in the podocytes and the renal capillary cells, which leads to proteinuria and kidney disease over time. It can lead to early onset stroke, hypertrophic cardiomyopathies, and arrhythmias, specifically bradyarrhythmias or malignant ventricular tachyarrhythmias. It can lead to gastrointestinal problems, which are frequently misdiagnosed as irritable bowel syndrome. Angiokeratomas are a very classic finding.

These are these purple raised spots that are classically described in a swim trunk distribution, which means it is underneath the bathing suit area, which means you have to disrobe your patients sometimes to see them. Although they're classically described in a swim trunk distribution, they can be all over the body, including around the outside of the lips, on the hands, et cetera. So they have a varied distribution, but classically, they are seen in increased concentrations underneath the bathing suit area or in the general region.

It also leads to hypohidrosis, so patients sometimes can complain of not sweating, and as such, they get overheated playing sports. However, although hypohidrosis of the classical females can actually have hyperhidrosis and have increased sweating due to autonomic dysfunction caused by the Fabry disease. They cause corneal opacities or sometimes called as corneal whorls. That's why ophthalmologists will diagnose these and send them. Corneal whorls do have a differential diagnosis, including hydroxychloroquine-induced corneal whorls.

Amiodarone can also do the same thing. It can lead to tinnitus and vertigo and can also lead to hearing loss. So let's just talk about some of the studies that were presented at the WORLD meeting in 2025 and talk about a study specifically on Fabry knowledge. So, this study was done in the United Kingdom to assess the awareness and knowledge of recognition of non-Fabry healthcare providers regarding Fabry disease in the United Kingdom. So, the design of this study was a online survey conducted with 84 non-Fabry healthcare providers, including general practitioners, anesthetists, neurologists, and opticians.

And what you can see is that 32% of them were unaware of Fabry disease. 10% or only 10% reported good knowledge about Fabry disease. But even knowing that or having an awareness of Fabry disease, 89% had never encountered a Fabry patient or at least had thought they had never encountered a Fabry patient. As we know, that the diagnosis can be elusive. So the conclusions were awareness and knowledge of Fabry disease among non-specialist healthcare providers remains low. That really highlights the need for improved education and targeted training to enhance early recognition and diagnosis of Fabry disease.

All right, so let's talk about the clinical trials that were presented at WORLD. And we can start with the Pegunigalsidase Alfa study. So, this abstract was really to look at the long-term safety and efficacy of Pegunigalsidase Alfa at two milligrams per kilogram every four weeks. Typically, Pegunigalsidase is prescribed at one milligram per kilogram every two weeks. This was to look at the prolonged administration, so every four weeks. So the design, this was a five-year extension study of the BRIGHT trial participants. In order to get into the BRIGHT study, you had to have a stable EGFR.

Specifically, your EGFR slope or your annualized EGFR slope could not have been greater than two mils per minute per 1.73 meter squared per year. So that is a very stable kidney population. So there were... if you look, there were 29 people that were evaluated in this. Males had a slope of negative 2.4, and ADA-positive males had a slope of negative 2.6, whereas females had a slope of negative 1.8, and all participants that were ADA-negative had a slope of negative 1.8.

So what this interpretation is is that females and males, and females who are ADA-negative. So all females had a slope that stayed less than negative two, which is very, very stable, and all participants who were ADA-negative had a slope of negative 1.8, which was stable for the study. However, those that were ADA-positive and specifically ADA-positive males had a slope that was negative 2.6, which is slightly higher than the inclusion criteria to be in the study.

So the conclusions are that Pegunigalsidase Alfa at two mg/kg every four weeks was well tolerated over greater than three years with stable plasma lyso-Gb3 level pain, quality of life measures. The EGFR slope remained stable in ADA-negative patients, males and females, but was more negative in ADA-positive males. So the take-home is ADA-positive males need more investigation to evaluate whether or not this dosing pattern is enough to keep the kidney function stable.

So next study that we're going to talk about, very exciting gene therapies in Fabry disease, multiple studies going on in gene therapy with Fabry disease. Obviously, many of us are excited just because of the promise or the possibility of doing a one-dose infusion and then never having to come back for infusions. Patients are excited about this too, but we have to do the studies to evaluate efficacy. This study is the 4D-310 study. So, this is to evaluate the safety and efficacy of 4D-310. 4D-310 is a cardiotropic adeno-associated gene therapy or adeno-associated virus gene therapy.

And the goal, since it was a cardiotropic AAV vector, was to evaluate the cardiac function in quality of life in patients who had received this therapy. So this is an ongoing Phase I and II trial with the single IV dose of 4D-310. And what you can see here is that the results of this abstract or what was presented, that the interim results showed that there were improvements in the peak use of oxygen that's graded

as the, VO2 improvements in global longitudinal strain as it relates to cardiac outcomes, and improvements in the cardiac quality of life scale with this study.

So that is the take home, that at least in the patients who were dosed with 4D-310, that there were some improvements specifically as it relates to cardiac outcomes. So more to follow through this gene therapy company. All right. The next study we'll talk about is the ST-920 study. This study was to assess the safety and efficacy and immunogenicity of ST-920, which is an adeno-associated virus which is liver tropic in adults with symptomatic Fabry disease. This was an ongoing Phase I-II study, which was called the STAAR trial.

There were 31 participants in the study who received the ST-920 gene therapy. What you can see is all enzyme or all patients who were on ERT actually successfully discontinued ERT by September of 2024, all patients had lyso-Gb3 reductions, and interestingly, many patients had a marked decrease in anti-drug antibodies after treatment. So the conclusions of this was that ST-920 is well tolerated. It increases alpha-galactoses, alpha-activity, reduces lyso-Gb3 and does enable ERT withdrawal. The next study we'll discuss was the SRT AL01211 abstract.

SRT stands for Substrate Reduction Therapy. Substrate Reduction Therapies inhibit glucosylceramide synthase, which blocks the conversion of ceramide to globotriaosyl ceramide or lyso-GL3, which is the disease-causing substance in Fabry disease. They're interesting therapies because they're oral therapies instead of IV, and they are not mutation-specific. So this study was to assess the safety and pharmacodynamics and preliminary efficacy of substrate reduction therapy in treatment-naive males. So 16 males actually received either 30 milligrams or 60 milligrams of AL01211.

And the findings were in the 16 males, was that there were significant reductions in GL1, GL3, lyso-GL3, and there were some clinical improvements in kidney function. So more to follow on all SRTs, but on AL01211. So let's move on to real-world studies. So one real-world study that was presented at the WORLD meeting was the accelerated infusion of agalsidase-beta in Fabry disease. So agalsidase-beta is typically infused at a rate no faster than one and a half hours per the FDA insert. This study was really to evaluate the safety and tolerability of faster administrations of agalsidase-beta, as many patients will tell you that they would like their infusion to go faster if at all possible.

So this is an ongoing Phase IV, open-label, single-arm study enrolling 14 patients between the ages of two and 65. And what you can see is that six patients actually were able to get down to an infusion rate of 20 minutes. Two classic male patients actually are down to 40-minute therapies, which is roughly half the fastest dose that was previously allowed. So the conclusions was that agalsidase-beta infusions as short as 20 minutes appear safe in ERT-experienced patients, which supports a potential protocol adjustment to reduce treatment burden. As we get more data, this may be an option moving forward.

So the next study we want to discuss is the patient-reported outcomes in the followME Fabry Pathfinders Registry. This was a real-world study to evaluate patient-reported outcomes in patients with Fabry disease, receiving migalastat, using the followME Fabry Pathfinders Registry. This was a prospective observational study analyzing the patients who had filled out the BPI, the FABPRO-GI, and

the TSQM are all patient-reported outcome tools in Fabry patients. And these were done in patients who had been on the migalastat for greater than two years.

The conclusion in these 86 patients that were evaluated was that pain, gastrointestinal symptoms, and treatment satisfaction remained stable over 36 months. So, the next study we'll talk about is tolerability and infusion-related reactions in patients switching to Pegunigalsidase Alfa. So, this study was to assess tolerability in fusion-related reactions in Fabry patients who switched from agalsidase-beta to Pegunigalsidase Alfa in the US Expanded Access Program.

So the design of this study was, it was a retrospective medical review of four patients with Fabry disease, three males, one female with greater than five years of enzyme replacement therapy who switched in the Extended Access Program from agalsidase-beta to Pegunigalsidase Alfa because they were not tolerating low agalsidase-beta as per the provider who switched them. So patient switching. What they found was that there was a reduced need for pre-medications. No corticosteroids were used. Two of three shortened their infusions to 60 to 90 minutes with only one mild infusion-related reaction.

So the conclusions of this abstract was that patients switching to Pegunigalsidase Alfa experienced fewer infusion-related reactions, reduced pre-medication use in shorter infusion times, suggesting improved tolerability in this patient population compared to their previous therapy of agalsidase-beta. So, next, we'll talk about the disease severity outcomes in Pegunigalsidase Alfa-treated patients. This was done by Hughes et al. What was done, they evaluated a 24-month change in disease severity using the Mainz Severity Score Index in patients with Fabry disease treated with Pegunigalsidase Alfa.

So, these were 87 patients that were treated with Pegunigalsidase Alfa over three clinical trials. Some were ERT-naive, and some were ERT-switch. And what they found was that ERT-naive patients showed a reduction in disease severity while ERT-switch patients maintained stable MSSI scores over a 12-month with a trend towards improvement at 24 months. So very similar to what we saw with the BALANCE trial, which is that the ERT-switch patients actually maintained the level of EGFR decline. Similar to that, patients were on ERT before and then switched to Pegunigalsidase Alfa treated patients... or who switched to Pegunigalsidase Alfa maintained their MSSI score.

So let's talk about the cardiovascular abstracts as they relate to Fabry disease presented at WORLD. So, first, we'll talk about the stroke risk reduction with agalsidase-beta treatment. The objective of this study to assess the stroke incidence in patients with Fabry disease treated with agalsidase-beta versus untreated patients in the Fabry registry. So the design, it was a matched cohort analysis, one-to-one treated versus untreated. There were 52.4% male, 68.3% were of the classic phenotype to estimate your stroke risk.

So, as you can see here, the median follow-up was 5.8 years in the treated population. It was 3.3 years in the untreated. And what you'll see is there was a 0.36 lower risk in the treated population versus the untreated Fabry population. So the conclusion was agalsidase-beta treatment may lower risk... stroke risk in patients with Fabry disease, with findings consistent across multiple adjustments. Now, we'll talk about quality of life studies in Fabry disease. So, let's talk about gender disparities in Fabry disease care.

So the objective of this study was to assess the experiences, healthcare perceptions, and challenges faced by females living with Fabry disease across North America and Japan. So, this was a patient-developed survey completed by 138 female respondents from the US, Canada, and Japan. And what you can see is there are differences in the responses of these females based on the countries that they live in with one of the most interesting differences is that in Japan, 89% of females, their top concern was disease inheritance.

Whereas in the US and Canada, the top concern of the females was the symptoms they were experiencing. So, the conclusions of study was female patients with Fabry disease report disparities in healthcare, support lack of healthcare provider understanding, and significant mental health issues and family planning concerns. This really highlights the need for improved healthcare provider education and gender-equitable care, which is very important Fabry disease because the phenotypic variation in females make them very difficult, A, to diagnose in the first place. And B, once you get a diagnosis, given how wide display is of the presenting symptoms, difficult to manage and decide on treatment. This study was to determine the long-term impact of migalastat on quality of life and adolescence with Fabry disease. Should be noted that migalastat is FDA-approved for the treatment of adults with Fabry disease in the United States. But we wanted to look at this in adolescence specifically. So the objective... So the design of this study was a Phase 3b, two-stage, open-label, multicenter study with an ongoing open-label extension.

Patient-reported outcomes were measured using the pediatric health and pain questionnaire. 22 people were enrolled, which were 10 males, 11 females. 11 had been on enzyme replacement therapy previously. The conclusion of the study was that migalastat treatment led to improvements in gastrointestinal symptoms, paresthesias, and overall quality of life, with positive trends observed regardless of prior ERT status. The next study is an assessment of clinical depression in patients with lysosomal storage diseases. The design of this study was a cross-sectional study of 44 lysosomal storage disease patients.

21 of these were females completing the Beck's Depression Inventory during routine clinical visits between March and June of 2024. Should be noted that 54% of these patients had Fabry disease, 27% had Gaucher disease, 66% of them were on therapy. The conclusion is that clinical depression is prevalent among lysosomal storage disease patients, often undetected in face-to-face consultations, highlighting the need for routine psychological assessments using the validated tool of the Beck's Depression Inventory.

Now, we'll talk about Clinical Pearls. So the Clinical Pearls are the take-homes.

So first on the clinical trial data, we have a lot of therapies that are under investigation, including substrate reduction therapy. We mentioned three gene therapy studies, which had promising data and enzyme replacement therapies that are changing the way that we think about how we treat Fabry disease and specifically have the hope of giving patient... patients many options on how to treat their disease. The take-home on the real-world abstracts that were presented was, once again, we continue to try and make things better for our Fabry patients.

A study showing that we could have reduced infusion times with agalsidase-beta. Migalastat is well tolerated after 36 months of therapy with stable symptoms in the followME Registry. And then, patients who were not tolerating agalsidase-beta, who switched to Pegunigalsidase Alfa actually had reduced pre-medications, reduced infusion reactions, and shorter infusion times in these real-world studies. So many things going on to continue to move the dial for our Fabry patients. Some other Clinical Pearls.

On the cardiovascular side of things of Fabry disease, we talked about how agalsidase-beta significantly reduces stroke risk in Fabry disease patients. On a quality-of-life perspective, we talked about how females definitely have different views of their most important symptom depending on the country that they are from, but also report disparities in healthcare and healthcare provider understanding of their disease, which means that we have to do a better job of educating about Fabry disease symptoms in two healthcare providers because of the phenotypic variation that we see in Fabry females.

And then, finally, awareness of Fabry disease continues to lack. In the UK study, 32% of providers had never even heard of Fabry disease, and 90% had never seen a Fabry patient. So we continue to have to educate healthcare providers on this disease that can be very, very debilitating but has treatments available.