Transcript Details
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Fabry Disease: Further Considerations in Selecting a Treatment Option

Announcer:
Welcome to ReachMD.

This medical industry feature is titled “Fabry Disease: Further Considerations in Selecting a Treatment Option.” This program is intended for US healthcare professionals only and contains promotional content prepared in part by, and is sponsored by, Sanofi Genzyme.

Here’s your host, Dr. Charles Turck.

Dr. Turck:
Fabry disease is a progressive, genetic disorder that, when undiagnosed and unmanaged, can cause multisystemic damage and even reduce life expectancy by approximately 20 years in men[1] and 15 years in women.[2] On today’s program, we’ll review the latest clinical outcome data and real-world evidence that has resulted in the 2021 Fabrazyme full approval.

This is ReachMD, and I’m Dr. Charles Turck. Joining me today is Dr. Joseph William Ray, an Associate Professor of Pediatrics and Director of Medical Genetics at the University of Texas Medical Branch, Department of Pediatrics in Galveston, Texas.

Dr. Ray, thanks for being here today.

Dr. Ray:
Thank you for having me!

Dr. Turck:
To start, Dr. Ray, can you give us a brief overview of Fabry disease?

Dr. Ray:
Sure. Fabry disease is a progressive, genetic disorder caused by variants in the galactosidase-alpha or *GLA* gene resulting in complete or partial deficiency in α-Gal A enzyme activity, which can lead to the accumulation of glycolipids-globotriaosylceramide, or GL-3, in the lysosomes.[3]

I typically describe Fabry disease as a disease of the vascular system, particularly the capillaries. So, everywhere capillaries are located, patients may experience symptoms there. There are lots of capillaries inside the brain, so we may see problems with the brain like strokes; there are lots of capillaries inside the heart, so we may see problems inside the heart like conduction defects or a breakdown of the heart tissue; there are lots of capillaries inside of the kidneys, so we may see kidney decline that could result in end stage renal disease; and then there are lots of capillaries in the skin, the eyes, so on and so forth. The GL-3 accumulation begins in utero and progresses silently throughout a patient’s lifetime, resulting in impaired cellular function in multiple organs, even causing irreversible damage to vital organs such as the kidney, heart, and brain, and even premature death.[4,5]

The signs and symptoms of Fabry disease vary across organ systems, genders, and ages. Some of the early symptoms of Fabry disease, starting as early as childhood, may include hearing loss, pain, gastrointestinal disturbances, hypohidrosis, or other symptoms.[3] As the disease progresses, renal impairment and cardiac dysfunction may occur, and we often see an increased risk of developing fatal complications such as end-stage renal disease, stroke, cardiac fibrosis, arrhythmias, and premature death.[3,4]

Dr. Turck:
Thank you for that Dr. Ray! But before we dive more into this conversation, let’s just take a moment to review the indication and

important safety information for Fabrazyme, a product manufactured by Sanofi Genzyme.

Announcer:

INDICATION AND USAGE

Fabrazyme® is indicated for the treatment of adult and pediatric patients two years of age and older with confirmed Fabry disease.[6]

Stay tuned to hear the full Important Safety Information at the end of this program.

Dr. Turck:
Now with that background in mind, can you tell us about why you choose Fabrazyme for your patients?

Dr. Ray:
Personally, I have a lot of experience with Fabrazyme, about 12 years. I feel like I have a good understanding of how it works, and I feel comfortable tackling any complications that may arise from taking it.

I've seen good results from it. Fabrazyme has over 18 years of real-world experience and a well-established safety profile.[6] It's currently used by over 5000 patients worldwide.[7] It's the only enzyme replacement therapy, or ERT, indicated for patients two years of age and older and has shown long term efficacy and safety. And another reason why I choose Fabrazyme is because it can be used in patients regardless of genotype, disease severity, or level of enzyme activity.[6]

Dr. Turck:
Following up on that Dr. Ray, how do you decide when to initiate Fabrazyme treatment for your patients, and is there a difference in how you make that decision between male and female patients?

Dr. Ray:
Well, one thing that I always consider when thinking about starting ERT for my patients is the impact on their quality of life.

With regards to males and females, what's different is the timing of the symptoms.[3] Males tend to develop symptoms very early on in life, within their first or second decade, and females tend to develop symptoms later on.[8]

For males, once I've established a diagnosis, we start treatment immediately,[3] because men with Fabry disease are at a significantly increased risk of morbidity and mortality,[9] and by the time the diagnosis is made, we can reasonably conclude that they likely have some end organ damage already.

As for my female patients who are diagnosed with Fabry disease, they've either had a long history of very vague symptoms that their doctor never associated to Fabry disease, or they were diagnosed because they had a family member who was diagnosed with Fabry disease, and then have since learned that they also have it.

So, with my female patients are trying to balance between controlling their disease and impacting their quality of life. I'll work together with my female patients to determine when we should start on ERT. When it comes to symptoms that she is complaining about, like neuropathy, pain in her hands and feet, inability to sweat, or having heat intolerance, I'll explain that starting treatment sooner rather than later is going to be very helpful. If I see organ damage on her surveillance labs, I'll send her off for imaging and start having serious conversations about initiating treatment.

It's important to note and to stress to your patients that even though this is an X-linked genetic disease, females with Fabry disease are not just carriers. Even if they feel "fine", the disease can progress silently and can lead to life-threatening events like LVH, stroke/TIA, or even end stage renal disease.

That's why it's important to keep following up with Female patients, and to encourage your female patients to keep up with their regular check-ups and routine labs - even if they seem to be asymptomatic.

Dr. Turck:
With the recent 2021 Fabrazyme label update, we know that some important clinical outcome data have become available. Let's review that data. Starting with Study 2, where clinically significant event outcomes were evaluated, what can you tell us about that?

Dr. Ray:
In Study 2, a randomized, double-blind, placebo-controlled, multinational, multicenter study, evaluated 82 patients, 72 males and 10 females, with Fabry disease, all naïve to enzyme replacement therapy.[6] Of the 82 patients, 51 and 31 patients were randomized to the Fabrazyme and placebo groups, respectively.[6] Patients were randomly assigned to receive Fabrazyme 1 mg/kg or placebo every other

week for up to 35 months, with a median follow-up of 18.5 months.[6] The primary efficacy endpoint was the time to first occurrence of a clinically significant event, as defined as renal, cardiac, or cerebrovascular event, or death.[6]

The results showed that 28 percent of Fabrazyme-treated patients experienced a clinically significant event, compared to 42 percent placebo-treated patients so, a smaller percentage of patients in the Fabrazyme treatment group experienced a clinically significant event.[6] The hazard ratio between the two groups was 0.57, with a 95% confidence interval of 0.27 and 1.22, and a p-value of 0.14.[6]

Dr. Turck:
Additionally, there's also Study 5, a long-term observational study that has contributed to the 2021 label update. Dr. Ray, what can you tell us about that study?

Dr. Ray:
So Study 5 assessed the rate of decline in renal function, or the eGFR slope, in patients with Fabry disease aged 16 years and older, where 122 patients who were treated with Fabrazyme were matched to a historical cohort of 122 untreated patients.[6] The median age when symptoms first appeared was 10 years, the median age at diagnosis was 26 years, and the median age at Fabrazyme initiation was 35 years.[6] Study 5 results showed the mean slope of eGFR for the Fabrazyme-treated patients as -1.5 mL/min/1.73 m^2/year and for the untreated group as -3.2 mL/min/1.73 m^2/year, with the estimated difference in the mean slope of eGFR as 1.7 mL/min/1.73 m^2/year.[6]

Dr. Turck:
Given these clinical outcomes, what are some takeaways you'd like to share with our audience?

Dr. Ray:
My main takeaway would be that an earlier diagnosis is important because it can result in earlier management of symptoms and disease-related complications with proper management and routine monitoring.

As I'd mentioned earlier, Fabrazyme has been around for over 18 years with a well-established safety profile and recent data shows that it has similar efficacy in the pediatric population and the adult population, as well as similar safety profile.[6] Also, this is the only Fabry treatment that's approved in the pediatric patient population of two years of age and older and it can be used in any patient regardless of genotype or disease severity.[6]

Dr. Turck:
That's a great way to round out our review of the 2021 Fabrazyme label update.

I want to thank my guest, Dr. Joseph Ray, for helping us better understand the latest Fabrazyme clinical outcomes data.

Dr. Ray, it was great speaking with you today.

Dr. Ray:
Thank you for having me!

Dr. Turck:
I'm Dr. Charles Turck. And before we close, let's take a moment to review some important safety information.

Announcer:

INDICATION AND USAGE
Fabrazyme® is indicated for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease.[6]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Anaphylaxis and Hypersensitivity Reactions

In clinical trials and postmarketing safety experience with Fabrazyme, approximately 1% of patients developed anaphylactic or severe hypersensitivity reactions during Fabrazyme infusion.[6]

Life-threatening anaphylactic and severe hypersensitivity reactions have been observed in patients during Fabrazyme infusions.[6]

- Reactions have included localized angioedema (including swelling of the face, mouth, and throat), bronchospasm, hypotension,

generalized urticaria, dysphagia, rash, dyspnea, flushing, chest discomfort, pruritus, and nasal congestion.[6]
- Interventions have included cardiopulmonary resuscitation, oxygen supplementation, IV fluids, hospitalization, and treatment with inhaled beta-adrenergic agonists, antihistamines, epinephrine, and IV corticosteroids.[6]
- If anaphylactic or severe hypersensitivity reactions occur, immediately discontinue administration of Fabrazyme and provide necessary emergency treatment.[6] Because of the potential for severe hypersensitivity reactions, appropriate medical support measures should be readily available when Fabrazyme is administered.[6]

In clinical trials with Fabrazyme, some patients developed IgE antibodies or skin test reactivity specific to Fabrazyme.[6]

- Higher incidences of hypersensitivity reactions were observed in adult patients with persistent anti-Fabrazyme antibodies and in adult patients with high antibody titer compared to that in antibody negative adult patients.[6]
- Physicians should consider testing for IgE antibodies in patients who experienced suspected hypersensitivity reactions and consider the risks and benefits of continued treatment in patients with anti-Fabrazyme IgE antibodies.[6] Rechallenge of these patients should only occur under the direct supervision of qualified personnel, with appropriate medical support measures readily available.[6]

Infusion-Associated Reactions

In clinical trials with Fabrazyme, 59% of patients experienced infusion-associated reactions, some of which were severe.[6] Infusion-associated reactions are defined as adverse reactions occurring on the same day as the infusion.[6] The incidence of infusion-associated reactions was higher in patients who were positive for anti-Fabrazyme antibodies than in patients who were negative for anti-Fabrazyme antibodies.[6]

- In patients experiencing infusion-associated reactions, pretreatment with an antipyretic and antihistamine is recommended.[6] Infusion-associated reactions occurred in some patients after receiving pretreatment.[6]
- If an infusion-associated reaction occurs, decreasing the infusion rate, temporarily stopping the infusion, and/or administrating additional antipyretics, antihistamines, and/or steroids may ameliorate the symptoms.[6]
- If severe infusion-associated reactions occur, immediate discontinuation of the administration of Fabrazyme should be considered, and appropriate medical treatment should be initiated.[6] Severe reactions are generally managed with administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen when clinically indicated.[6] Because of the potential for severe infusion-associated reactions, appropriate medical support measures should be readily available when Fabrazyme is administered.[6]
- Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion-associated reactions.[6] Monitor closely patients with compromised cardiac function if Fabrazyme is administered to these patients.[6]

ADVERSE REACTIONS

- Common adverse reactions reported (≥20% and >2.5% compared to placebo) were upper respiratory tract infection (53% vs 42%), chills (49% vs 13%), pyrexia (39% vs 22%), headache (39% vs 28%), cough (33% vs 25%), paresthesia (31% vs 18%), fatigue (24% vs 17%), peripheral edema (21% vs 7%), dizziness (21% vs 8%), and rash (20% vs 10%).[6]

Please see full Prescribing Information for Fabrazyme.

Announcer:
This program was sponsored by Sanofi Genzyme. If you missed any part of this discussion, visit ReachMD.com/industry-feature. This is ReachMD. Be Part of the Knowledge.

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