Fabry Disease Research Highlights

Hello. My name is Derralynn Hughes. I'm professor of Experimental Hematology at University College, London. I work in the Lysosomal Storage Disorders Unit at the Royal Free London NHS Foundation Trust. I'm going to review some of the research highlights relating to the Fabry disease at the World Symposium 2020. A learning objective is to describe the latest research related to Fabry disease, better understand the condition, the best amount of people with Fabry disease.

Well, 2021 was quite different to any of our previous symposia. World Meeting is an annual meeting, focused on lysosomes storage diseases. It usually takes place as a five day live event in February, each year. However, this year, of course, due to the pandemic it was a virtual meeting and so quite different in its relationships of the speakers and the meetings and the general discussion. Since Fabry disease requires a team approach, involving all areas of the multidisciplinary team of cardiology, nephrology, and neurology, we felt it was important to discuss some of the World highlights related at the virtual meeting so that the wider team could have access to this information. There were a number of presentations related to Fabry disease, and we'll start with some new insights into the natural history that came from the Fabry outcome survey.

FOS is now 20 years old and has recruited more than 4,000 people with Fabry disease from 144 centers throughout the world. Data of that whole cohort over 20 years. So it's a small decline in the renal function in the eGFR slope and a small increase in the LVMI slope. Over 20 years of enzyme replacement therapy.

We also look at the mean age of symptom onset versus diagnosis, and it still shows us that such an onset occurs many years before diagnosis. And therefore the opportunity for making an earlier diagnosis and an impact through earlier treatment remains to be yet fully optimized. For conclusions of FOS, provides insights into the natural history, it's a treatment efficacy, but really does show us that there is an opportunity to both diagnose and to make treatment earlier for patients with Fabry disease.

Equally, there were studies looking at the impact of starting late of enzyme replacement therapy on Fabry disease. This study for the multidisciplinary team at UCLA looked at various aspects of physical health and quality of life in 26 patients receiving enzyme replacement therapy. Most of the patients had common symptoms for Fabry disease, including your neuropathic pain, cardiac involvement, and angiookeratomas. Others had some more uncommon findings, such as pulmonary involvement, lymphedema and hearing loss. The study found, that enzyme replacement therapy as expected, improved levels of plasma GL-3, but of note, in those patients who started enzyme replacement therapy later, the decline in renal dysfunction and health-related quality of life continues.

So what are the opportunities for earlier diagnosis of Fabry disease, which might therefore help us to start enzyme replacement therapy or other Fabry specific therapies more punctually. Earlier Fabry disease, earlier onset Fabry disease, or classical Fabry disease, may be easier to diagnose, in fact, by consideration that classical triad of symptoms of angiokeratoma, hyperhidrosis and corneal opacities. Later onset poverty disease is often associated with involvement of a single organ, and in fact therefore
may not declare itself until there's already significant organ damage. For example, renal dysfunction or cardiomyopathy. And therefore even here, there's a need to reduce the time to diagnosis from the start of organ manifestations.

We know three possible studies using technology to try to instigate an earlier diagnosis of patients with Fabry disease. The first of these studies use routinely acquired hospital data. 2 million people coming to one of the UK hospitals, the team look for patterns of symptoms, which might allow early diagnosis of patients.

The second study also looked for patterns such as pain, as an early symptom to Fabry disease in the German pain registry. In the final study, we note that there was an artificial intelligence algorithm designed to compare data from nearly 5,000 patients with Fabry disease, with over a million patients who did not have Fabry disease. And this AI model appeared to create an algorithm which risks. So in the final study, our model of artificial intelligence was developed comparing data from over 5,000 patients with Fabry disease, with over a million patients who didn't have Fabry disease. This AI algorithm appeared to create a model with a high diagnostic efficiency with up to 180 fold enrichment in the identification of patients who had Fabry disease.

Once a patient with Fabry disease is diagnosed, there's often family screening, cascade screen, which leads to the diagnosis in other patients related to the index case who may not themselves at that stage actually have symptoms which might be indicative of treatment. And therefore it's important that those patients are fully evaluated and followed serially perhaps over a number of years until they meet the criteria for Fabry specific treatment. It's therefore important to understand the natural history and the staging of some of the manifestations of Fabry disease. And this work from Augusto, et al looked at the staging of cardiomyopathy by imaging through cardiac MRI of the hearts of patients with Fabry disease. Suggesting that there were a number of stages that a patient might progress through.

Therefore, giving us insights of possible early features on which treatment might be initiated. They describe myocardial blood flow, global longitudinal strain, T1 and T2 relaxation times. We found that patients who had low T1 generally had a higher LVMi and other changes in the ECG. Whereas patients who had normal T1, said sometimes have microvascular impairment as subtle T2 elevation and other different changes in the ECG. On this basis, they predict various stages of cardiomyopathy, a pre LVH state, where they could detect storage, the storage stage, followed by left ventricular hypertrophy and inflammation, and then followed ultimately by fibrosis and impairment of conduction.

In addition to making an earlier diagnosis and allowing treatment for patients with Fabry disease, we witnessed a developmental program of new treatments for patients with Fabry. Linhart, et al presented data from the BRDIGE study, which is a study looking at switching patients from agalsidase alpha to a new pegylated enzyme replacement therapy called pegunigalsidase alpha. On average, the patients were 45 years old. There was a mixture of classic and non classic patients. And the patients had an estimated eGFR annualized decline of minus 5.9 mLs per minute. And that was roughly balanced between males and females. After switching, you can see that in many patients, the rate of decline actually decreased, and you can see here, the overall rate of decline decreased and also in males and females.
Another modality of treatment, which is currently being explored is gene therapy. This has been used either as ex vivo or in vivo gene therapy. And there were a number of different presentations related to gene therapy for Fabry disease. There were two presentations, one ST-920 looking at in vivo gene therapy with AAV2/6 vector, and another one by Thomas, et al, an ex vivo gene therapy using AVR-RD-01 lentiviral construct, which is given to autologous stem cells, which are then transplanted into the patient. We look forward to seeing further data on both of these studies as the treatments mature, and we become to understand further the role of gene therapy in the treatment of patients with Fabry disease. So finally, in this year of the COVID-19 pandemic, I'd like to discuss two studies, which relate to the impact of COVID-19 on patients with Fabry disease. The first is a study presented by Don Laney and colleagues who looked at real-world experience of 22 patients with Fabry disease who had COVID-19 infections. It's actually two patients dying.

Both of these patients had serious cardiac and renal problems associated with Fabry disease. They put together a scheme map which showed that many patients have low risk of COVID 19 reactions. And these are the patients who essentially don't have organ involvement. Whereas for those patients who have open involvements in terms of heart and kidney problems, they may well have a high risk of COVID-19 consequences and therefore need to take appropriate precautions in terms of self isolation and possibly vaccination, for example. COVID has also had an impact on clinical trials. For those patients who are already enrolled in a clinical trial, it’s been important that we’ve been able to continue with regular monitoring and implementation of the study, or many studies we've changed to remote visits. Frey, et al looked at the impact of COVID-19 in the Lucerastat study of oral substrate reduction therapy in Fabry disease. And they looked at our ability to change to remote visits with oral treatment, which was shipped to the home.

In this study, the data analysis did not reveal any differences between the Lucerastat and frequently used COVID-19 medication. So in conclusion, a wide range of clinical studies in relation to Fabry disease were presented at World 2021. This ranged from a discussion of 20 years of enzyme replacement therapy treatments through fostering a natural history data collection and the registry collection of patients receiving enzyme through that study. We've also seen improvements in diagnosis, an increased understanding in the role of early diagnosis and early treatment. We've seen studies evolving on the use of chaperone therapies and enzyme treatment, but also now studies on newer treatments, such as enzyme replacement, new substrate reduction and gene therapies in development. There were also presentations this year about co-morbidities and staging of the Fabry disease, and also the impact of COVID not only on the treatment of patients with Fabry disease and on their outcomes, but also on our delivery of clinical trials. As with all storage disorders, it's important to note that the team approach to treatment is needed.

Thank you for your attention.