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SPEAKER: In order to treat correctly a disease, we should understand the pathogenesis. And Fabry disease is a rare disease. There is no adequate animal model. So we have some gaps there. However, we understand very well the pathogenesis of our related metabolic proteinuric progressive kidney disease, which is diabetic nephropathy.

And we know from diabetic nephropathy that we have two different problems. The first problem the metabolic defect that we should treat. But the second problem is that, once kidney injury has developed, it may progress independently from the metabolic defect.

So conceptually, we need two different therapeutic approaches to diabetic kidney disease and to Fabry nephropathy. First, treat the metabolic defect, but additionally, if there is already kidney injury, if there is already pathological albuminuria, please treat the albuminuria.

So what tools do we have to treat the metabolic effects in Fabry nephropathy? We have enzyme replacement therapy, agalsidase beta, and we have the chaperone, migalastat. On top of that, we should add renal angiotensin system blockade. There is evidence from clinical trials that, if you are able to lower albuminuria to lower proteinuria with renal angiotensin system blockade, on top of agalsidase beta, the slope of the loss of glomerular filtration rate will be slower.

OK, so treat the metabolic defect, and additionally, add nephroprotection. Why is this important? Because we [INAUDIBLE] from kidney biopsy in childhood, that already in childhood, there is evidence of irreversible glomerular injury, of glomerular scarring, of focal segmental glomerulosclerosis, which means irreversible glomerular scarring. So we should treat as early as possible.

We have data from clinical trials, long-term clinical trials, that agalsidase beta is effective in preventing the progression of kidney disease. And we know this because of a phase IV clinical trial with primary endpoint events, agalsidase beta versus placebo. This trial was under-powered, only 80 patients, so there was a 50% decrease in the incidence rate of severe events. But the P was 0.06, so it was not statistically significant.

However, we have more recent data from a trial called the Canadian Fabry Disease Initiative. It was a 10-year trial, so long-term trial, that allowed to assess the impact of therapy on severe kidney events such as dialysis, doubling of serum creatinine, or nephrotic range proteinuria. And in this Canadian Fabry Disease initiative trial, agalsidase beta, as compared not with placebo-- as compared with another, rather, enzyme replacement therapy, which is agalsidase alpha-- agalsidase beta was able to decrease the incidence of severe renal events by fourfold.

Fourfold decrease in the incidence of severe renal events. So now we know for sure that agalsidase beta, in the long term, preserves renal function. What about migalastat? Well, we have not such long experience with migalastat. We know that, as for agalsidase beta, migalastat made clear glycolipid deposits in [INAUDIBLE], but we don't have long-term experience.

So summarizing, we have clinical trial evidence that agalsidase beta may preserve renal function in Fabry nephropathy. We also know that when there is evidence of kidney disease, as for diabetic kidney disease, we should add nephroprotective therapy. We know that correcting the metabolic defect will not reverse kidney injury because the end result of Fabry disease in the kidneys is glomerular scarring, and scars are not recovered.

So we should be treating as early as possible in order to keep renal function as high as possible. If we start therapy with a high renal function. It will remain high. If we start therapy with a low renal function, it will remain low. The impact of therapy is not reversing the issues but is slowing the progression.