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Alport Syndrome - Early Detection?

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The lecture about the scientific progress in Alport syndrome with its possibilities of early diagnosis and pre-emptive therapy will illustrate the bright perspective of nephrology: ***personalized medicine - the future of nephrology -*** *with assessment of individual therapeutic response and prognosis, will be based on genetic characterization and on our growing biochemical understanding of common pathways in kidney fibrosis.*

This broad future of nephrology can be wonderfully demonstrated using the example of the hereditary type IV collagen disease Alport syndrome as a model disease of chronic renal fibrosis: the gene defect in Alport syndrome makes it impossible for the podocytes to form an intact glomerular basement membrane. However, the mature, mechanically strong glomerular basement membrane develops slowly after birth. This opens a "window of opportunity" for early genetic diagnosis in Alport syndrome, before the kidney damage has entered the vicious circle of kidney scarring. More than 30 years ago, the growing biochemical and molecular biological understanding of the disease processes in our patients with Alport syndrome made it possible to bring research from the bedside to the laboratory bench: The high conservation of the structure of type IV collagen in all mammals, for example, made extremely accurate animal models possible. For the past 25 years, we have been looking for therapeutic approaches in these animal models. In 2003, the success story of pre-emptive therapy with ACE inhibitors begun in mice with Alport syndrome. The impressive results from the laboratory bench, the delay of onset of end-stage kidney disease (ESKD) by 100%, were confirmed in 2012 by observational studies of the European Alport registry: depending on the early start of therapy, defined as proteinuria without major loss in eGFR, ESKD can be delayed by decades and life-expectancy can be improved. The breakthrough in evidence-based therapy, however, only came with the world's first randomized placebo-controlled intervention study, EARLY PRO-TECT Alport, which was published in 2020. The ACE-inhibitor Ramipril in children with Alport syndrome two years and older is safe and – very similar to the animal model - seems to be effective in delaying progression of micro-albuminuria. The efficacy data from EARLY PRO-TECT Alport, though, are not significant in the classical statistical definition. This is why we started the Alport XXL project in order to further improve clinical evidence using a Bayesian approach of evidence synthesis.

Wonderful international cooperations, including dear colleagues such as Professor Hee Gyung Kang from ***Seoul National University****, build the broad basis for constant scientific exchange on pre-emptive therapy in children and young adults. Current and future therapies will be discussed including SGLT2-inhibitors, mineralocorticoid receptor antagonists, podocyte-protective approaches, and more curative genetic strategies such as gene-editing, read-through or exon-skipping* ***(Figure 1)****.*

Together with the audience, the lecturer will develop the path of early genetic diagnosis and multi-targeted therapy with the claim that, in the majority of cases of Alport syndrome, ESKD can be delayed by decades, if not for lifetime ***(Figure 2)****.*