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Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy

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Alport syndrome inevitably leads to end-stage renal disease and there are no therapies known to improve outcome. Here we determined whether angiotensin-converting enzyme inhibitors can delay time to dialysis and improve life expectancy in three generations of Alport families. Patients were categorized by renal function at the initiation of therapy and included 33 with hematuria or microalbuminuria, 115 with proteinuria, 26 with impaired renal function, and 109 untreated relatives. Patients were followed for a period whose mean duration exceeded two decades. Untreated relatives started dialysis at a median age of 22 years. Treatment of those with impaired renal function significantly delayed dialysis to a median age of 25, while treatment of those with proteinuria delayed dialysis to a median age of 40. Significantly, no patient with hematuria or microalbuminuria advanced to renal failure so far. Sibling pairs confirmed these results, showing that earlier therapy in younger patients significantly delayed dialysis by 13 years compared to later or no therapy in older siblings. Therapy significantly improved life expectancy beyond the median age of 55 years of the no-treatment cohort. Thus, Alport syndrome is treatable with angiotensin-converting enzyme inhibition to delay renal failure and therapy improves life expectancy in a time-dependent manner. This supports the need for early diagnosis and early nephroprotective therapy in oligosymptomatic patients.

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This article is dedicated to the children and young adults included in our registry who died because of limited access to renal replacement therapy.

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Evaluation of microhematuria and microalbuminuria is common in everyday clinical practice as they are important early signs for chronic kidney disease (CKD). CKD substantially increases the risk of cardiovascular events and death.[1] Renal fibrosis is the end point of most CKDs.

Therefore, in addition to controlling hypertension,[2] therapy targeted at the prevention of renal fibrosis may be of value. Renal fibrosis due to Alport syndrome (AS) is seen in association with end-stage renal disease (ESRD) in children and young adults.[3] AS is a hereditary nephropathy characterized by progressive renal failure, sensorineural deafness, and typical ocular changes.[4] AS serves as a model of understanding progression of chronic renal fibrosis in mice[5–7] and humans.[8] The disease is caused by mutations in type IV collagen genes, leading to an abnormal composition of the glomerular basement membrane.[9] In all, 85% of Alport families have an X-chromosomal and 15% an autosomal trait of inheritance.[10] Abnormal composition of the glomerular basement membrane due to AS leads to extensive matrix deposition, inflammation, and fibrosis.[5,6] These are major components of progressive renal failure in literally all CKDs. AS inevitably leads to ESRD during adolescence or early adulthood, and ~50% of patients develop ESRD by the age of 20 years.[11]

Early diagnosis in children with AS with isolated hematuria opens a 'window of opportunity' for early intervention. Currently, there are no causal therapeutic options that are proven to delay renal failure in AS.[8] Angiotensin-converting enzyme inhibition (ACEi) has been shown to reduce proteinuria in Alport patients[12] and to delay renal failure in Alport mice,[5] suggesting that it may be of value as an effective treatment to delay renal failure in humans.[7] To test this we established the European Alport Registry to collect data over several generations of Alport families across Europe. Small children with AS first develop microscopic hematuria, proceeding to microalbuminuria, overt proteinuria, and impaired renal function, and end up with ESRD. These different steps of disease enabled us to assess if earlier introduction of ACEi at earlier degrees of disease is more effective than later therapy in delaying the time to dialysis and improving life expectancy. Our results might have the potential for generalization of the use of early nephroprotective therapy in all patients with Alport syndrome in everyday clinical practice.

RESULTS

Primary end point 'age at start of renal replacement therapy'

A total of 283 patients were followed for a mean of more than two decades (Figure 1). The mode of inheritance was within the expected range (Table 1).[10]

All 109 *noT* patients (red curve, Figure 2) were related to treated patients. Because of the genotype–phenotype correlation in AS,[3] the *noT* group with the same genotype minimized selection bias toward 'more benign' mutations in the

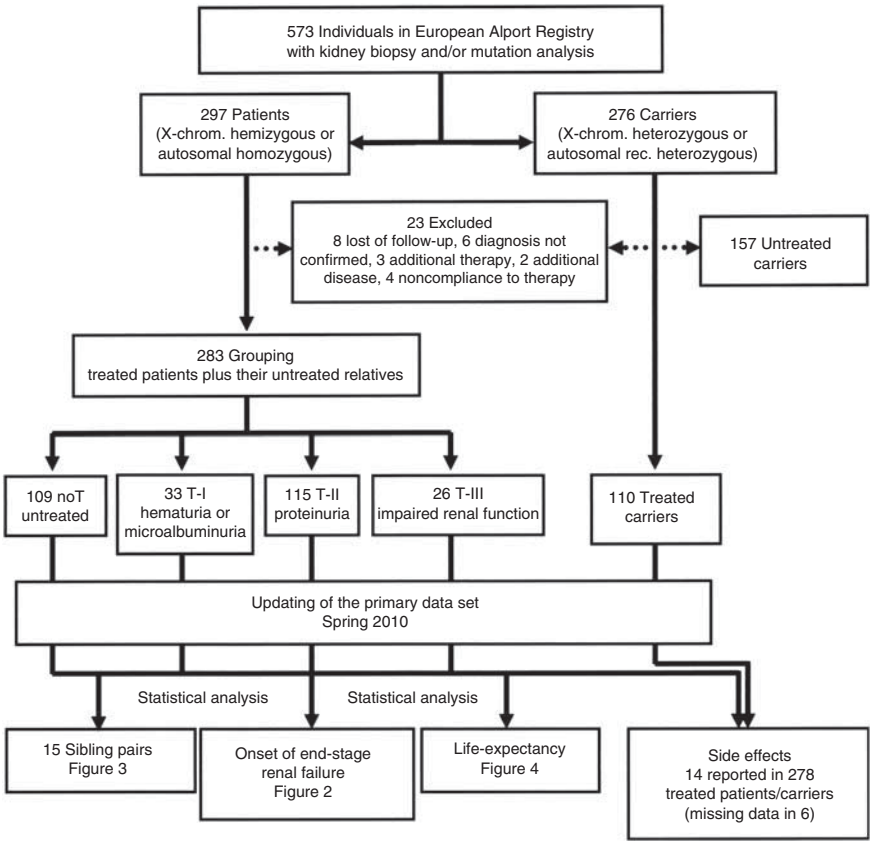

Figure 1 | Screening, assignment, follow-up, and selection for statistical analysis. Work flow of screening, assignment, updating data, and statistical analysis of Alport syndrome (AS) patients. Heterozygous carriers of Alport mutations were included in analysis of side effects of medication, but excluded from all other analyses. X-chrom., X-chromosomal.