

# Still an unmet need: New therapeutic targets in Alport syndrome

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Alport syndrome (AS) is a hereditary type IV collagen disease that leads to progressive proteinuria, renal fibrosis, and kidney failure. Depending on the mutated gene and the pattern of inheritance, there are three types of AS. Mutations in COL4A5 cause severe disease in males and a disease of variable severity (but usually much less severe) in females. Mutations in COL4A3 and COL4A4 are the cause of the autosomal forms of AS. Homozygous or compound heterozygous mutations in COL4A3 or COL4A4 are the cause of autosomal recessive AS (ARAS), while a single mutation in either of these genes causes autosomal dominant AS (ADAS).

Having only one mutation in COL4A3 or COL4A4 can cause a phenotype that ranges from nothing (i.e. some parents of children with ARAS) to haematuria alone or to proteinuria and subsequent renal failure on top of haematuria. Over the past several years it has become increasingly apparent that more patients reach end-stage kidney [disease](#) (ESKD) due to ADAS than due to classical X-linked AS or ARAS, even though this progression occurs at a much older age. The seminal determinant of disease progression in AS logically seems to be the amount of damage in the glomerular basement membrane (GBM).

A surrogate pathological marker may be tubulointerstitial fibrosis, which has been recognized as the key feature in progressive renal damage leading to ESKD. The glomerular disease and the podocyte stress response lead to the secretion and distribution of profibrotic chemokines and cytokines, which are the main causes of interstitial fibrosis and

tubular atrophy. Progression from haematuria to microalbuminuria and progression from microalbuminuria to overt proteinuria represent very important steps in the course of AS. As for many renal diseases, the primary endpoint for AS clinical trials is or will be the decline in GFR.

"But similarly to other renal diseases, this is probably too late an endpoint to make a significant impact on the course of the disease," explains Professor Roser Torra, Barcelona/Spain, main author of the review published in NDT today. "Theoretically, treatment prior to the appearance of [renal fibrosis](#) offers more promising long-term renal outcomes. GBM aspect and degree of fibrosis on renal biopsy as well as proteinuria could be excellent endpoints for clinical trials."

At present, there is no curative treatment for AS, so all males with X-linked disease and all males and females with ARAS, as well as a certain percentage of patients with ADAS, will ultimately show progression to ESKD. The only recommended treatment nowadays for this disease is RAAS (renin-angiotensin-aldosterone system) blockade. Currently RAAS is being tested in children even before the onset of proteinuria.

Currently there is an ongoing trial using bardoxolone and another using anti miRNA21 is expected to start soon. Other drugs under study for AS are paricalcitol, lipid-lowering agents, epidermal growth factor receptor inhibitors, chaperones, stem-cell based therapies, inhibitors of STAT3, etc.

"A specific disease-modifying therapy for AS remains an unmet need, but I am sure this will change, because AS has become a very attractive disease for pharmaceutical companies to target," emphasizes Professor Torra and gives five reasons:

1. it is an excellent model of chronic kidney disease (CKD) with proteinuria and fibrosis that may be extrapolated to other more

common causes of CKD

2. any drug approved for this disease will have an orphan drug designation with its consequent benefits, such as shortened approval timeline, financial incentives, and a period of market exclusivity
3. the number of patients to be treated will be substantial, AS being the second more frequent inherited kidney disease after ADPKD; patients are young and have very few comorbidities, which facilitates [clinical trials](#)
4. there is no approved treatment for AS

**More information:** Roser Torra et al, New therapeutic options for Alport syndrome, *Nephrology Dialysis Transplantation* (2019). [DOI: 10.1093/ndt/gfz131](#)

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