ALPORT SYNDROME

About time—treating children with Alport syndrome

Judy Savige

Can treatment delay end-stage renal disease in children with Alport syndrome? New guidelines have been provided based on our ability to identify individuals at risk of early-onset renal failure and on evidence for blockade of the renin–angiotensin system that has been derived from Alport patient registries, other renal diseases and animal studies.

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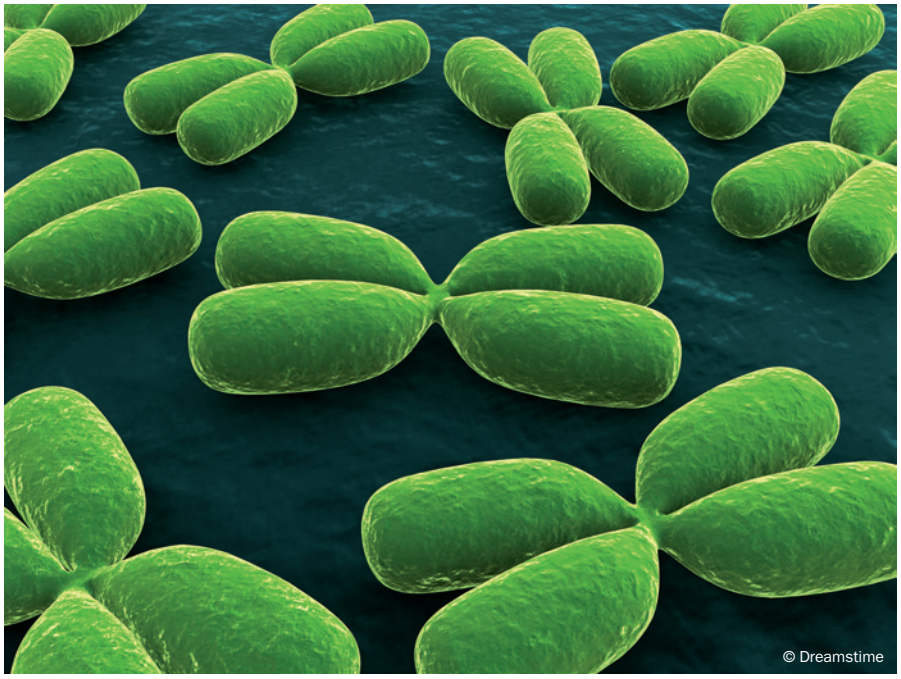
All medical practitioners who care for those with Alport syndrome have watched the relentless deterioration in renal function in patients with this disease. In response, Kashtan *et al.* have provided a protocol for treating the children who are at greatest risk of early-onset renal failure, that is, before the age of 30 years.[1] This article incorporates guidelines on monitoring for proteinuria, when to start treatment (with angiotensin-converting-enzyme [ACE] inhibitors, angiotensin-receptor blockers and an aldosterone antagonist) and target levels of proteinuria after treatment. The authors concede that widespread adoption of their guidelines mean the definitive study of the efficacy of ACE inhibitors in Alport syndrome might never occur as the pool of children who are eligible for clinical trials of potential therapies for Alport syndrome will be reduced. They nevertheless encourage medical practitioners to submit clinical data from patients treated according to this protocol to an Alport registry that will enable evaluation of the guidelines and their further refinement.

Alport syndrome affects one in 10,000 individuals and is one of the most common causes of inherited renal failure. Most families have X-linked disease with mutations in the *COL4A5* gene. Affected males typically present in childhood with hematuria, and later develop microalbuminuria and proteinuria. 50% of patients have end-stage renal disease (ESRD) by the age of 25 years and 90% of patients by the age of 40 years.[2] Females usually have much milder disease than do males because of the effect of X chromosome inactivation, and only 15% of females develop renal failure by the age of 60 years. Autosomal recessive inheritance with mutations in *COL4A3* or *COL4A4* accounts for fewer than 20% of patients. Clinical features of these patients are identical to those in males with X-linked disease, with most developing early-onset renal failure.



In the past decade, there have been two major advances in the treatment of Alport syndrome: it is now possible to predict individuals at risk of early-onset renal failure and evidence exists that blockade of the renin–angiotensin system delays the onset of ESRD. Most patients with early-onset renal failure are males with X-linked disease. Age at onset is similar for all affected men within a family,[3] and is more common with gene rearrangements, large deletions, and splicing and nonsense mutations.[2,3] It is more difficult to predict at-risk females on the basis of their genetic mutation, but the presence of proteinuria is a poor prognostic sign.[4] Most patients with recessive disease also develop early-onset renal failure, and, again, proteinuria is associated with a poor prognosis. Treatment is now possible in these poor prognosis groups. Data from animal studies,[5,6] the European Alport Registry[7] and from patients with other renal diseases[8,9] all suggest that blockade of the renin–angiotensin system delays the onset of end-stage renal failure and improves survival in patients with microalbuminuria and possibly even before microalbuminuria develops.

Thus, these guidelines recommend annual monitoring of boys with X-linked disease at risk of early-onset renal failure, from 1 year of age or from the time of diagnosis. Treatment with ACE inhibitors is advocated where there is overt proteinuria or a urine protein–creatinine ratio >0.2, and treatment should be considered where there is microalbuminuria. The authors suggest using ramipril because of its efficacy in

mouse models[6] and low toxicity in children, but this is a class effect, and the authors provide a list of other agents and equivalent doses that can be considered. If proteinuria persists above the target levels, the dose of ACE inhibitor should be increased, and an angiotensin-receptor blocker, and possibly an aldosterone antagonist, added. In girls, treatment should be considered when there is microalbuminuria, and treatment instituted with the onset of proteinuria. For males and females who are likely to develop late-onset renal failure, after the age of 30 years, treatment is started with the onset of proteinuria. These guidelines imply that individuals with autosomal recessive disease who have albuminuria should be treated too.

> “Guidelines based on expert opinion and preliminary results ... have a role in clinical medicine...”

The management of Alport syndrome is broader than simply delaying ESRD. Many of the authors of this article are also members of a team that has prepared comprehensive guidelines for the diagnosis and management of Alport syndrome. These guidelines emphasize genetic testing, determining the mode of inheritance, monitoring, managing extrarenal complications, consideration of other causes of the Alport phenotype, treatment in adults as well as children, who else to test within the family, who can be a renal donor, and transplantation.

The use of ACE inhibitors is neither specific for the treatment of Alport syndrome nor new. Inhibition of the renin–angiotensin system is widely used to delay the onset of ESRD in patients with diabetes and those without diabetes who have proteinuria.[8,9] What is new about the Kashtan *et al.* guidelines is the recommendation to screen children with Alport syndrome from an early age on the basis of their genetic risk, and institute treatment when they develop proteinuria or microalbuminuria.

Initiating treatment at the onset of microalbuminuria may, however, not be soon enough. An analysis of a subset of patients in the European Alport Registry suggested that starting ACE inhibitors before the onset of microalbuminuria delayed ESRD and further lengthened survival.[7] A phase III clinical trial addressing the timing of initiation of treatment of Alport syndrome is currently underway (EARLY PRO-TECT).[10]

Proteinuria levels generally decrease after the commencement of ACE inhibitors, and later return to, or even exceed, pretreatment levels.[6] This observation is hinted at by the hierarchy of suggested treatments in this article, but is not addressed directly.

One of the limitations of evidence-based medicine is the need to wait for the evidence. Guidelines based on expert opinion and preliminary results that avoid the delays and expense of clinical trials have a role in clinical medicine, but they must continue to be reviewed and updated. The guidelines by Kashtan *et al.* support making an early diagnosis of Alport syndrome and identifying the mode of inheritance and mutation, as treatment delays the need for renal replacement therapy, and potentially improves patients' quality of life and life expectancy because of the high mortality associated with renal failure.[7]

Adoption of these guidelines means that many children with Alport syndrome worldwide will be screened, monitored and treated uniformly, and this article emphasizes the usefulness of disease registries and the ways in which collaborations between patients, clinicians and researchers can advance our understanding and management of a disease.

The University of Melbourne, Northern Health, 185 Cooper Street, Epping, VIC 3076, Australia.
jasavige@unimelb.edu.au

Competing interests
The author declares no competing interests.

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