lin and postulated that this inhibited protein C activity. The further activation of NFκB in this system could suppress the expression of the thrombomodulin gene and further decrease anti-inflammatory mechanisms.\textsuperscript{15}

DISCLOSURES

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REFERENCES


See the related article,”Anti-Endothelial Cell Autoantibodies Selectively Activate SAPK/JNK Signalling in Wegener’s Granulomatosis,” on pages 2497–2508.

Fabry Nephropathy and the Case for Adjunctive Renal Therapy

Christoph Wanner and Frank Breunig

University Clinic, Division of Nephrology, Department of Medicine, University of Würzburg, Würzburg, Germany


Proteinuria in advanced Fabry nephropathy does not respond to enzyme replacement therapy (ERT) alone using recombinant agalsidase-α or -β. In this issue of \textit{JASN}, Tahir et al.\textsuperscript{1} describe a series of patients who had Fabry nephropathy and achieved sustained reductions in proteinuria and stabilization of kidney function after treatment with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) combined with ERT. Because proteinuria has emerged as an important risk factor for progression of kidney disease and ACEI/ARB therapy is effective in lowering proteinuria in other renal diseases, the result by Tahir \textit{et al}. is important, incremental news for this group of patients.

Replacement of a deficient enzyme with recombinant protein has been a turning point for the clinical management of lysosomal storage disease. Gaucher disease in the 1990s was the first lysosomal storage disease for which ERT provided exceptional clinical results, and only after a few treatments over a
short period. This success led to high expectations when approximately 10 yr later, Fabry disease became the second lysosomal storage disease to be treated with ERT. Pivotal trials showed remarkable results with respect to reduction of pain and substantial cellular clearance of accumulated globotriaosylceramide (GL3). Five years later, we have to acknowledge that in specific clinical situations, such as advanced Fabry nephropathy, ERT alone is not a panacea. Proteinuria, up to 3 g/d, does not respond to ERT alone, and, happily, adjunctive antiproteinuric therapy seems useful in altering the course of progressive kidney injury.

The kidney in Fabry disease is a key modulator in overall prognosis and response to therapy. Rapid cellular clearance of GL3 and improvement in clinical outcome are not always possible by starting ERT at any point in time. Recent data suggest that the degree of organ involvement at the time when enzyme replacement is initiated is a crucial factor. In patients with organ damage, fibrosis, and advanced levels of GL3 storage, Fabry-related end points may occur despite ERT, and level of kidney function may be just as good an indicator of the stage of disease as any other.

Still, we have incomplete knowledge of kidney pathology and the determinants of renal progression after storage of GL3 within lysosomes. Observations from renal biopsies in patients with Fabry disease demonstrate rapid clearance of GL3 in the vascular endothelia over 6 mo but is delayed in podocytes; proteinuria, up to 3 g/d, does not respond to ERT alone, and, happily, adjunctive antiproteinuric therapy seems useful in altering the course of progressive kidney injury.

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Still, we have incomplete knowledge of kidney pathology and the determinants of renal progression after storage of GL3 within lysosomes. Observations from renal biopsies in patients with Fabry disease demonstrate rapid clearance of GL3 in the vascular endothelia over 6 mo but is delayed in podocytes; even after 5 yr of ERT, some GL3 deposits are still present in these cells. Although effective reduction in proteinuria and stabilization of kidney function with ACEI/ARB suggest that Fabry nephropathy is susceptible to local antagonism of the angiotensin system, as other kidney diseases, a link among proteinuria, GL3-positive podocytes, and angiotensin remains speculative. All other cardiovascular protective measures also need evaluation.

Because ACEI/ARB target various general pathways in the development of chronic kidney disease, it seems surprising that there had been no attempt to investigate these combination of drugs with ERT until now. Nearly half of all men who have Fabry disease with estimated GFR > 60 ml/min per 1.73 m² demonstrate significant proteinuria, > 300 mg/d (Fabry Registry). Proteinuria predicts progression in patients with Fabry nephropathy, and once patients are on the slope of GFR decline, the annual loss of renal function varies from 4 to 12 ml/min. That all of these patients should receive antiproteinuric therapy is an approach not recognized in Fabry disease until now.

Many physicians believe that ACEI/ARB therapy is not feasible in patients with low or low-normal BP. Indeed, our previous observations suggested that patients often stop ACEI once they experience Fabry symptoms. We must acknowledge that perhaps we could have done better. Tahir et al. achieved impressive results by careful titration of ACEI/ARB therapy to stabilize kidney function at a GFR decline of 0.23 ml/min per yr. Even though baseline BP, especially in men, is not typically elevated but low, it is possible to achieve sustained reductions in urinary protein excretion and stabilization of GFR with careful titration of angiotensin antagonists.

The general therapeutic efficacy of ERT has also been variable, ranging from a good response to no effect. Factors that may have an impact on the lack of response are incompletely understood. Probably irreversible end-organ damage plays a role, but differences in uptake of the enzyme or the occurrence of neutralizing antibodies may influence the outcome. Antibodies toward the enzyme preparations develop frequently in male patients because they often do not express residual enzyme activity and are therefore immunologically intolerant. Previous studies reported emergence of IgG antibodies in 56 to 88% of male patients who received either agalsidase-α or -β. These antibodies may have neutralizing capacities that attenuate the effect of ERT on GL3 clearance. Because the response to ERT is variable even in the absence of antibodies, it is difficult to determine whether high-titer neutralizing antibody translates into a lack of clinical response. Studies that show a good relationship between the amount of enzyme administered and the clinical response in relation to the titer of unwanted antibody are lacking. Therefore, ERT dosing may be an important issue that needs to be addressed in patients with more advanced kidney involvement. Although administration of larger amounts of the enzyme has been successfully implemented in other diseases, such as hemophilia A, it is unclear whether it may serve to accelerate the rise in antibody formation in the immunologically intolerant patient.

The article by Tahir et al. demonstrates what an experienced clinical scientist always wants to observe by looking carefully at a rare disease. Even when only a few patients are studied, we can learn important lessons from such disorders. There are still some uncertainties around these new observations because of small sample size, but a larger trial is under way to confirm proof of principle. There is reason to hope, however, that adjunctive therapy can stabilize kidney function in advanced Fabry nephropathy with the combined use of ACEI/ARB and ERT.

DISCLOSURES

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REFERENCES


See the related article, “Antiproteinuric Therapy and Fabry Nephropathy: Sustained Reduction of Proteinuria in Patients Receiving Replacement Therapy with Agalsidase β,” on pages 2609–2617.