Is Regression of Chronic Nephropathies a Therapeutic Target?

Giuseppe Remuzzi and Andrea Remuzzi

Mario Negri Institute for Pharmacological Research, Bergamo and Unit of Nephrology, Ospedali Riuniti di Bergamo, Italy

Most kidney diseases lead to progressive deterioration of renal function, but the rate of progression differs among different disease types and even among individual patients with the same disease. Experimental studies and clinical research over the last few decades have identified several plausible mechanisms for progression of renal disease in various animal models and in human disease. These observations have led directly to studies establishing the fact that loss of renal function can be limited by certain antihypertensive medications (1). Thus, drugs that counteract the action of angiotensin II (AII)—the angiotensin-converting enzyme (ACE) inhibitors and the AII receptor antagonists—modify glomerular hemodynamics, lower proteinuria, and slow the rate of disease progression (2). Whether these drugs given in higher doses than those required to normalize BP can not only slow or halt progression but also induce regression of established glomerulosclerosis and tubular interstitial lesions has been debated. Evidence of reversal of proteinuria and glomerulosclerosis by combining a low-protein diet with an ACE inhibitor was first provided by Marinides et al. in 1990 in the puromycin aminonucleoside rat model (3). Ten years later, attention was again drawn to this topic by the work of Ma et al. (4). Although at that time glomerular structural changes were still considered irreversible, these authors showed regression of glomerulosclerosis in aging rats given an AII receptor antagonist. In this study, reversal of glomerular and vascular lesions was associated with modulation of plasminogen activator inhibitor-1 (PAI-1). The efficacy of AII antagonism in inducing regression of structural changes has also been demonstrated in a genetic model of progressive kidney disease, the male Munich Wistar Fromter (MWF) rat (5,6). In these rats, which develop glomerulosclerosis and tubular interstitial lesions, functional and structural changes had already developed. Following both treatments, or several combinations of them, sclerotic changes numerically decreased in only 4 wk from biopsy (8 wk) to autopsy (12 wk). This effect was attributed to the significant decrease in tissue inhibitor of metalloproteinase (TIMP-1). The limited effect on glomerular sclerosis was associated with reduced proteinuria, supporting the hypothesis that whenever a treatment is effective in reducing protein excretion, it is also effective in inducing regression of glomerulosclerotic changes.

Evidence that regression of glomerulosclerosis can occur emerges also from clinical observations. In diabetic nephropathy, Mauer and coworkers have demonstrated that ten years after pancreas transplantation, signs of diabetic glomerulopathy were effectively reduced, likely as a consequence of normalization of hyperglycemia (10). However, renal function continued to deteriorate. In this context the results of the Ramipril Efficacy in Nephropathy (REIN) study (11) in proteinuric non-diabetic nephropathies are of some interest. Among 78 patients treated with the ACE inhibitor, 10% exhibited an increase in baseline GFR during 6 yr of continued treatment, indicating functional regression of renal disease. Sixteen additional patients had stabilization of GFRs. More recently, dual blockade of the renin-angiotensin system by ACE inhibitors and AII receptor antagonists up-titrated to maximum tolerated doses

Published online ahead of print. Publication date available at www.jasn.org.

Address correspondence to: Dr. Giuseppe Remuzzi, Mario Negri Institute for Pharmacological Research, Via Gavazzeni 11, 24125, Bergamo, Italy. Phone: 39-035-319-888; Fax: 39-035-319-331; E-mail: gremuzzi@marionegri.it

Copyright © 2005 by the American Society of Nephrology

ISSN: 1046-6673/1604-0840
achieved a full remission of the nephrotic syndrome and stabilization of GFR in 27 of 37 patients who previously had, despite ACE inhibitor therapy, a progressive worsening of proteinuria and renal function (P. Ruggenenti, unpublished observation). In the remaining 11 patients, treatment achieved only partial remission of proteinuria, and GFR continued to slowly decline.

Taken together, this body of evidence indicates that, by mechanisms yet to be defined, the glomerular capillary network can sometimes undergo a process of both structural and functional regeneration. However, little is known at the moment about the processes responsible for these effects of AII antagonism (12). While some capillary segments may potentially regenerate and increase the functioning portion of glomerular capillary network, at the same time glomerulosclerosis can regress. However, we still do not have direct evidence that individual glomeruli affected by sclerosis completely recover following treatment, and this information is very difficult to obtain, as it is virtually impossible to follow in time structural changes of individual capillary tufts. Despite this caveat, however, there is evidence that regression of structural changes is based on the remodeling of extracellular matrix, a decrease in cell apoptosis, and probably, but as yet undemonstrated, the presence of stem cells in glomeruli. Experimental studies have contributed a lot, but from the clinical point of view the real goal of glomerular disease regression remains elusive. In particular, it is still a matter of controversy whether regression can be achieved in a consistent percentage of patients and to what extent. Even in those few instances in which effective regression of glomerulosclerosis has been consistently documented (4,5,8), quantitative information is lacking. Conventional evaluation of the number and extent of glomeruli exhibiting glomerulosclerosis, as measured by morphologic analysis of kidney tissue sections, does not tell us what fraction of the glomerular capillary network can effectively be restored to normal. There is evidence that estimation of the incidence and extent of glomerulosclerosis with serial-section analysis of entire individual glomerular capillary tufts may give results very different from conventional single-section morphology (13). Thus, while only an average of 29% of glomeruli were scored as affected by glomerulosclerosis in the adriamycin model on single sections, serial-section reconstructions revealed that 92% of glomeruli on average actually showed sclerotic changes. Similar results have been obtained in the analysis of human kidney biopsies (14). To accurately establish to what extent AII antagonism can effectively reduce the sclerotic areas, and the volume of glomerular capillary tuft eventually regenerated, more extensive investigation, focused at the individual glomerular level, is needed. Another important question to resolve is to what extent the observed regression of structural changes actually translates into effective improvement of kidney function. We know that, with adequate treatment, proteinuria can be effectively limited and, in some circumstances, even normalized. To the extent that proteinuria is a relevant factor for the progression of the disease (1,15), limiting protein excretion is expected to have beneficial effects on GFR, tubular water, and electrolyte reabsorption, as well as on excretion of uremic toxins.

There are however two outstanding issues which particularly need to be addressed. One is whether regression of renal lesions can be achieved in all progressive forms of glomerulopathies, or will only some types of renal diseases respond. Future clinical investigations will likely address this issue. The other question is whether, in the context of progressive diseases, regression of the lesions can potentially be achieved in a consistent proportion of patients or only in a minority. The answer to this will determine the clinical relevance of the above strategies. At present, there is limited information from which to draw conclusions. Experimental studies indicate that treatment of rats affected by glomerular diseases can induce regression of structural lesions consistently in a large majority of animals studied. However, human conditions are definitely more heterogeneous than experimental models. This heterogeneity may be related to different stages of the disease, association with different pathologic conditions including immunological processes, and differing potential of separate kidney tissues to repair or regenerate. Whether higher doses of ACE inhibitors or AII receptor antagonists can achieve more general and effective regression of renal disease is still a question that requires more investigation.

In conclusion, despite many uncertainties and as yet unknown factors, regression of human kidney disease now represents a realistic potential clinical target. Experimental evidence, including the study of Ma et al. in this issue and other work in progress, will likely soon delineate the mechanisms responsible for the beneficial effect of AII blocking agents and thereby more clearly define their therapeutic potential in human disease as well as ways to increase efficacy. A more complete understanding of these phenomena may also allow us to identify additional therapeutic interventions, other than antagonism of AII, that will help achieve even greater remodeling of glomerular and tubular structures accompanied by reversal of loss of kidney function.

References
6. Remuzzi A, Fassi A, Bertani T, Perico N, Remuzzi G: ACE inhibition induces regression of proteinuria and halts pro-


See related article, “Regression of Glomerulosclerosis with High-Dose Angiotensin Inhibition Is Linked to Decreased Plasminogen Activator Inhibitor-1,” on pages 966–976.