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Renoprotective Therapy in Patients With Nondiabetic Nephropathies

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Abstract

End-stage renal failure (ESRF) represents a major health problem. Early diagnosis and effective measures to slow or to stop renal damage are essential goals for nephrologists to prevent or delay progression to ESRF. Identifying mechanisms of progressive parenchymal injury is instrumental in developing renoprotective strategies. Protein traffic through the glomerular barrier is an important determinant of progression in chronic nephropathies and proteinuria is the best predictor of renal outcome.

At the moment, ACE inhibition is the most effective treatment in patients with chronic nondiabetic proteinuric nephropathies, reducing protein traffic, urinary protein excretion rate and progression to ESRF more effectively than conventional treatment. Low sodium diet and/or diuretic treatment may help to increase the antiproteinuric effect of ACE inhibitors by maximally activating the renin-angiotensin system. Intensified blood pressure control, whatever treatment is

employed, also enhances the antiproteinuric response to ACE inhibitors. However, since this is not always sufficient to normalise urinary proteins and fully prevent renal damage, additional treatments may be needed in patients poorly or not responding to ACE inhibitors. These may include angiotensin II receptor antagonists, non-dihydropyridine calcium antagonists and perhaps low doses of nonsteroidal anti-inflammatory drugs.

Preliminary data on multidrug treatments including these additional antiproteinuric agents are encouraging, but additional studies in larger patient numbers are needed to better define the risk/benefit profile of this innovative approach.

End-stage renal failure (ESRF), a too common final result of renal disease, is a major health problem. Its prevalence and incidence have rapidly increased in the last 2 decades; the costs of ESRF treatment have been approximately $12.3 billion per year in the US since 1995 and they are rising by 10% per year.[1] Thus, even in the world's richest countries, it will be difficult to ensure the funding for the future treatment of ESRF.

In this context, early diagnosis and the use of effective measures in order to slow, or possibly to stop, the progression of renal disease once the loss of function is established, are essential goals. This review approaches the problem of renoprotection from the point of view that chronic renal failure (CRF) evolves to ESRF through a series of common mechanisms which cause progressive parenchymal damage that seem to be relatively independent from the initial insult. Only by identifying these mechanisms is it possible to build a strategy which may ensure renoprotection.

1. Mechanisms of Chronic Renal Disease Progression

In the 1970s, experimental studies[2] led to the formulation of a unifying hypothesis for the progressive nature of renal diseases: the common pathway theory. This suggested that the reduction in nephron number, secondary to the initial insult, damages the intact remnant nephrons which suffer the consequences of the adaptive increases in glomerular capillary pressure and flow required to sustain renal function. These glomerular haemodynamic changes are detrimental in the long term, leading to renal functional and structural damage.

Therapies such as dietary protein restriction[3] and ACE inhibitors,[4] which attenuate such adaptive changes, effectively limit structural injury and slow renal function decline over time.

Animal and human studies have now shown that this process of progressive destruction of nephron units pivots around the impaired glomerular permselectivity to plasma macromolecules (proteins), secondary to long term glomerular hypertension. In fact, the high glomerular capillary pressure enlarges the radii of the pores perforating the glomerular membrane by a mechanism at least partially mediated by angiotensin II.[5] This alters the size selectivity of the barrier and allows an excessive ultrafiltration of plasma proteins which accumulate in the lumen of the proximal tubules.[6,7]

These abnormally filtered proteins may have intrinsic renal toxicity.[8] In fact, after endocytosis into proximal tubule cells, they contribute to renal interstitial injury through a complex cascade of intracellular events; protein overload causes lysosomal swelling and rupture followed by cytoplasm damage induced by lysosomal enzymes that then reach the renal interstitium. Moreover, protein reabsorption leads to an up-regulation of renal genes encoding vasoactive and pro-inflammatory molecules such as endothelin (ET)-1[9] and chemotactic cytokines such as monocyte chemotactic protein-1 (MCP-1)[10] and RANTES (Regulated upon Activation, Normal T Cell Expressed and Secreted).[11] In cultured cells these molecules are secreted toward the basolateral compartment of tubu-

lar cells giving raise to the inflammatory reaction,[8] ultimately causing renal fibrosis (fig. 1).

Of course, mechanisms other than modification of size selectivity may modulate protein transport through the glomerular barrier. These include configuration, deformability and charge selectivity.[12-14] However, there is no definitive answer regarding how the permeability of the glomerular barrier to proteins is modified and further studies are required to address this important issue.

Consistent with *in vitro* experiments is *in vivo* evidence that, in rat models of proteinuric nephropathy, the expression of renal genes encoding vasoactive and proinflammatory molecules are upregulated.[15-18] If the interstitial inflammatory reaction and the subsequent fibrosis in proteinuric chronic nephropathies were indeed a feature of protein overloading, limiting protein traffic or the effect of excessive tubular protein reabsorption should prevent or delay renal disease progression. This is precisely what happens in animals where both interstitial inflammation and progression of the disease can be limited by drugs that improve glomerular permselectivity, reducing proteinuria and filtered protein-dependent signals for mononuclear cell infiltration and extracellular matrix deposition.

One might argue that tubulo-interstitial inflammation, observed in proteinuric renal disease, is sustained by immunological mechanisms that are relatively independent of tubular protein overload and which resemble the mechanisms involved in chronic glomerular inflammation. Of interest, however, chronic tubular inflammation is also observed in non–immunologically-mediated proteinuric glomerulopathies such as experimental and

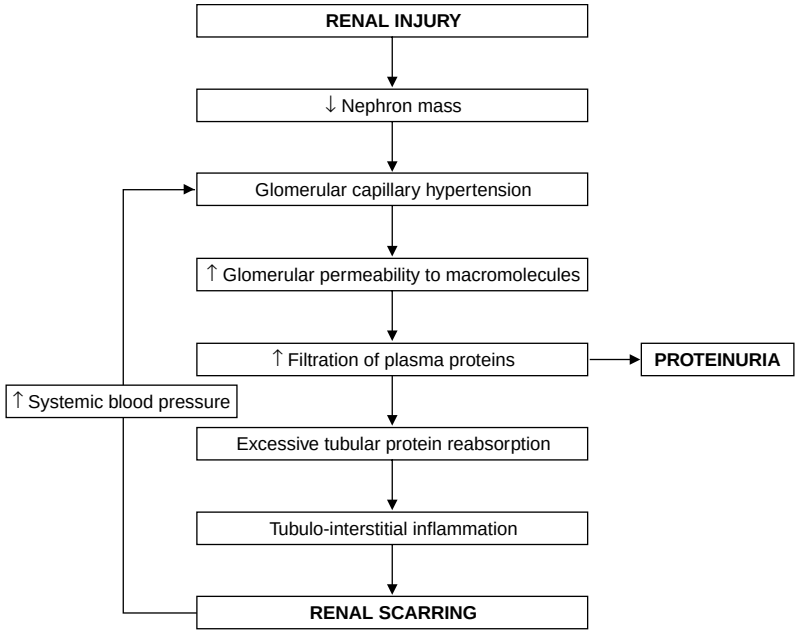

Fig. 1. Schematic representation of the impact of increased glomerular permeability to proteins on progressive renal damage. Excessive reabsorption of ultrafiltered proteins leads to a congestion of endolysosomes and endoplasmic reticulum in proximal tubular cells that may trigger excessive synthesis of vasoactive and inflammatory substances which contribute to fibroblast proliferation and interstitial inflammation, ultimately leading to enhanced extracellular matrix deposition and renal scarring. The consequent reduction in nephron mass, through enhanced systemic blood pressure, fuels a self-perpetuating cycle of nephron destruction culminating in uraemia. ↑ indicates increase; ↓ indicates decrease.

human diabetic nephropathy. This is an additional *in vivo* evidence that, in proteinuric chronic nephropathies, protein tubular overload plays a paramount role in the pathogenesis of tubulo-interstitial inflammation.

Results of clinical studies and clinicopathological correlations in patients with different forms of progressive proteinuric nephropathies indicate that the observations made in experimental models are relevant to understanding human disease.

In fact, many studies in patients with renal disease have found that more severe proteinuria is associated with a more rapid disease progression. Independently from the initial diagnosis, among 400 patients with nondiabetic proteinuric renal diseases, progression was slower in patients with urinary proteins less than 5 g/day whereas those with higher values had more rapid deterioration of renal function.[19]

In 840 patients with nondiabetic renal disease enrolled in the Modification of Diet in Renal Disease (MDRD) study,[20] proteinuria was the strongest predictor of renal outcome. Additional evidence of a contributory role of protein traffic in renal disease progression comes from the observation that in nephroangiosclerosis and diabetic nephropathy the onset of *de novo* proteinuria after a number of years of stable renal function is an indicator of subsequent renal function decline.

Moreover, the Ramipril Efficacy in Nephropathy (REIN) study[21] found that in patients with chronic nondiabetic proteinuric nephropathies, independently of the nature of the underlying disease, baseline urinary protein excretion rate was the best single predictor of renal disease progression. Thus, patients with baseline urinary protein excretion <1.9 g/24 hours had the lowest rate of glomerular filtration rate (GFR) decline and kidney failure (<5%) over 3 years of follow-up. Patients with nephrotic range proteinuria (>3.9 g/24 hours) lost >10 ml/min/1.73m^2 GFR per year with >30% kidney failure at 3 years.[22] Of interest, in this study, higher blood pressure predicted a faster GFR decline and a lower kidney survival only for a mean arterial pressure (MAP) >112mm Hg over the follow-up period. This suggests that uncontrolled hypertension may contribute to the acceleration of renal injury subsequent to enhanced protein traffic through the glomerular barrier. On the other hand, neither serum triglyceride nor serum cholesterol levels correlated with the decline in GFR and progression to ESRF over the follow-up period, suggesting a limited independent role for dyslipidaemia in the progression of chronic renal disease (CRD).

2. Renoprotective Treatments

Preliminary studies in a small number of patients found that any treatment that reduced urinary protein excretion in the short term effectively limited the progressive decline in renal function.[23] Further analyses in a large series of patients with chronic nondiabetic renal disease followed prospectively by repeated GFR evaluations found that blood pressure reduction produced significantly greater benefit on the rate of GFR decline in patients with higher baseline proteinuria. Even more interesting, in the same series, independently of the level of blood pressure and of the class of antihypertensive used, reduction of proteinuria was associated with a subsequent beneficial effect on the progression of renal disease.[20]

2.1 Reduced Protein Intake

Despite findings in rats with renal mass ablation and in animals with experimental diabetes mellitus and doxorubicin-induced nephropathy, that a low protein diet prevented proteinuria and renal injury,[24,25] confirmation of a beneficial effect of dietary protein restriction in clinical trials has been inconclusive because of deficiencies in their design or because changes in renal function were assessed only by measurements of serum creatinine levels, which may be affected by diet.

Recently, the MDRD study[20] found only a nonsignificant trend toward a slower GFR decline in patients on a very low protein diet (0.28 g/kg bodyweight per day), which is consistent with a moderate effect of very low protein intake or of the associated keto acid–amino acid mixture. Nonetheless,

there was no significant difference between the different diet groups in the time to the occurrence of end-stage renal disease.

Thus, available data do not support protein restriction as an effective treatment to slow disease progression in chronic nephropathies. However, it seems prudent to avoid a dietary protein intake in excess of 1 g/kg/day (it should be ideally around 0.8 g/kg/day) in patients with persistent heavy proteinuria and with chronic renal disease unless a high protein intake is specifically desired for short term management of malnutrition.

2.2 Antihyperlipidaemic Treatment

Hyperlipidaemia is common in patients with CRD, especially in those with nephrotic syndrome. In addition to accelerating the development of systemic atherosclerosis, experimental studies in animals suggest that hyperlipidaemia may enhance the rate of progressive glomerular injury.[26] In fact, cholesterol loading enhances glomerular injury and reducing lipid levels with an HMG-CoA reductase inhibitor slows the rate of progressive renal injury.[27,28] Moreover, the beneficial effect of lipid lowering may be additive to that of lowering blood pressure.

However, the clinical evidence on the role of controlling dyslipidaemia in preventing the progression of renal disease is still lacking; thus, the main goal of treatment of hyperlipidaemia in CRD is actually the prevention of atherosclerotic disease. In patients without cardiovascular disease, circulating levels of low density lipoprotein (LDL) cholesterol ≤130 mg/dL (≤3.36 mmol/L) should be achieved; for those with cardiovascular disease or other forms of atherosclerotic disease, LDL cholesterol values should be ≤100 mg/dL (≤2.59 mmol/L). Diet and bodyweight reduction may help to improve the lipid profile but often the use of HMG-CoA reductase inhibitors is necessary. ACE inhibitors often reduce serum lipids and the magnitude of these changes appears to be related to the degree of fall in protein excretion.

2.3 Tight Blood Pressure Control

The MDRD study,[20] in which patients with chronic nephropathies of various origin were randomly assigned to either conventional, <140/90mm Hg, or low blood pressure goal, <125/75mm Hg, found a correlation between lower follow-up blood pressure and slower GFR decline, which depended on the level of baseline proteinuria. In particular, the association between higher MAP and steeper decline in GFR began to become apparent at about 92mm Hg if proteinuria was more than 3 g/24 hours and at about 98mm Hg if proteinuria was between 0.25 and 3 g/24 hours. These findings led the authors to recommend considering the level of proteinuria when blood pressure goals are being set in patients with chronic nephropathy; in particular, they suggested a blood pressure goal of ≤125/75 and ≤130/80mm Hg, respectively, in patients with urinary protein excretion more or less than 1 g/day. The conventional goal of 130/85mm Hg is still acceptable for patients with proteinuria <0.25 g/day.

This study also assumed for the first time that, once close blood pressure goal is achieved, different antihypertensives are equally effective in reducing urinary protein excretion and slowing renal disease progression. This is in line with the recent evidence that greater the blood pressure reduction the less the antiproteinuric response depends on the class of antihypertensive employed.[8]

2.4 ACE Inhibition Therapy

2.4.1 Glomerular Barrier Dysfunction

Studies in diabetic and nondiabetic renal disease found that besides reducing systemic blood pressure, ACE inhibitors also reduced urinary proteins by improving the permselectivity of the membrane. Thus, in 10 patients with immunoglobulin (Ig)A nephropathy and clinical proteinuria,[29] 1 month of enalapril therapy significantly lowered fractional clearances of albumin and IgG and ameliorated size selective properties of the glomerular membrane measured by the clearance of neutral dextrans of different molecular radii; these changes were completely reversed after 1-month wash-out from ACE inhibition therapy and were not ac-

counted for by assumed changes in glomerular pressures. Evidence that calculated changes in membrane pore radii are unrelated to assumed changes in hydraulic pressure gradient across the glomerular membrane, suggests that the reduced filtration of circulating macromolecules associated with ACE inhibition therapy does not simply result from an hypothetical reduction in glomerular capillary pressure but must additionally derive from changes in intrinsic membrane permselective properties.[29]

2.4.2 Renal Disease Progression

A meta-analysis[30] of 10 studies in 1594 patients with nondiabetic renal disease found that ACE inhibitors were more effective than other antihypertensive agents in lowering urinary proteins and slowing the progression to ESRF but the mean decline in blood pressure during follow-up was greater in the ACE inhibitor as compared with the conventional therapy groups; thus, it could not be said whether the reduced risk of progression was due to the fact that ACE inhibitors lowered protein traffic or rather was a specific effect of better blood pressure control.

The ACE Inhibition in Progressive Renal Insufficiency (AIPRI) study,[31] included 583 patients with renal insufficiency caused by various disorders and found a lower risk of doubling baseline serum creatinine levels in patients receiving ACE inhibitor therapy with benazepril than in those receiving conventional therapy. However, again, a considerable difference in blood pressure between the 2 treatments left open the question of whether the renoprotective effect of benazepril was related to its antiproteinuric effect or to better blood pressure control. Among the patients in this trial, a majority had non-proteinuric chronic renal diseases with a remarkably slow progression rate and appeared not to benefit from ACE inhibitor therapy, at least during the study follow-up. Patients who did benefit from the treatment had urinary protein excretion of >3 g/day and the nephroprotective effect of the ACE inhibitor was related to its reduction of urinary proteins.[31] Thus, once again, these findings support the link between the renoprotective properties of a given drug and its ability to lower urinary proteins.

Unlike previous trials, the REIN study was designed to test whether glomerular protein traffic influenced renal disease progression and whether an ACE inhibitor (ramipril) was superior to conventional therapy, at comparable blood pressure control, in reducing proteinuria, limiting GFR decline and preventing ESRF.[21]

The REIN study[21] showed that among patients with baseline urinary protein excretion >3 g/24 hours, both the mean rate of GFR decline and the risk of reaching the combined end-point of doubling the baseline serum creatinine level or ESRF were significantly lower in the ramipril than in the placebo group. Of interest, a higher level of baseline urinary protein excretion was associated with a faster mean rate of GFR decline and with an higher risk of reaching an end-point in the placebo group but not in the ramipril group, which suggests that higher the proteinuria, the higher renoprotective potential of ramipril treatment.

The GFR decline in the ramipril group was associated with an early reduction in urinary protein excretion rate, which remained significantly lower than in the control group throughout the whole study. In both treatment groups blood pressure was comparable at baseline and remained similar during the entire follow-up period (with differences consistently below 2mm Hg), providing evidence that ramipril slowed renal function decline and halved the combined risk of doubling of serum creatinine level or ESRF through a renoprotective effect largely independent of changes in blood pressure (fig. 2). On the other hand, the finding that ramipril-induced reduction in urinary protein excretion rate was the only time-dependent covariate that predicted a lower rate of GFR decline and progression to ESRF, clearly indicated that renoprotection is linked to protein traffic reduction.[21]

The results of the REIN follow-up study[32] indicated that prolonged ACE inhibitor therapy slowed the rate of GFR decline and limited the progression to ESRF even more; of note, GFR almost stabilised and the risk of requiring dialysis was

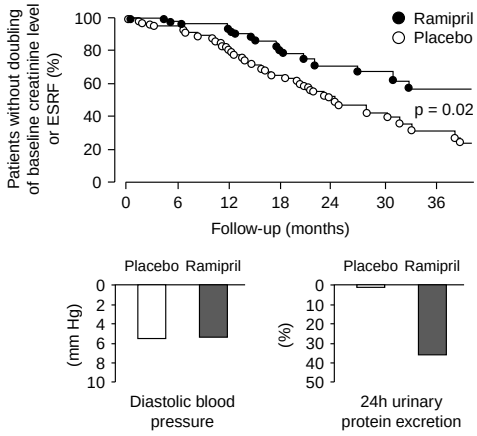

Fig. 2. Risk to reach the combined end-point of doubling serum creatinine levels or end-stage renal failure (ESRF) in the Ramipril Efficacy in Nephropathy (REIN) study, among patients with baseline urinary protein excretion ≥3 g/day. 58 patients reached this combined end-point: 18 in the ramipril and 40 in the placebo group (p = 0.02). At baseline, blood pressure was similar in the 2 treatment groups and remained comparable during the entire follow-up period, whereas urinary protein excretion decreased early, after 1 month, in the ramipril group and remained significantly lower than in the control group throughout the study period.

negligible in patients taking continued ramipril therapy for more than 36 months.

Recent data from this study[33] show that the tendency of GFR to decline with time in chronic nephropathies can not only be slowed but also reversed, even in patients with severe disease. Similar results have been obtained in patients with diabetic nephropathy[34] and in preliminary studies in experimental animals where early ACE inhibition therapy may reverse some of the glomerular and tubulointerstitial changes of remnant kidney nephropathy and sustain structural rearrangements aimed to increase the glomerular filtering surface by glomerular capillary neoformation.[35] Thus, both experimental and clinical data strongly suggest that long term ACE inhibitor therapy may lead to remission of CRD at least in some patients.

ACE inhibitor therapy was also renoprotective in patients with nondiabetic chronic nephropathies and non-nephrotic proteinuria[36] where it halved the risk of progression to ESRF and to persistent nephrotic range proteinuria compared with conventional antihypertensive treatment. In addition, urinary protein excretion decreased in the ACE inhibitor group but progressively increased in the conventional antihypertensive group. This led to a significant difference in urinary protein excretion rate between the 2 treatments that paralleled the different risk of progression to end-points. These results again support the hypothesis that reducing proteinuria is protective in the long term.

Moreover, patients with basal GFR of 45 ml/min/1.73m^2 or less had a high risk of developing ESRF and were protected from events by ACE inhibitor therapy, whereas those with a better preserved renal function had a very low risk of progression that was not substantially influenced by ramipril.[36] Among patients with basal GFR of 45 ml/min, 24-hour proteinuria above or below 1.5g identified 2 different rates of progression and response to therapy. The response to ramipril in patients with basal 24-hour proteinuria of ≥1.5g is consistent with data from patients with chronic nephropathies and 24-hour proteinuria ≥3g.

Of interest, a different gender response to ACE inhibitor renoprotection was been found in the REIN study.[37] Compared with men, women were faster progressors on conventional treatment but slower progressors on ramipril treatment. Thus, ramipril decreased GFR decline and events by 52 and 74%, respectively, in women and only by 19 and 40%, respectively, in men. This different response to ramipril translated into more proteinuria reduction in women than in men, despite comparable blood pressure control.

Analyses of the I/D (insertion/deletion) polymorphism of the ACE gene in the study group as a whole, found that the DD genotype was associated with more sensitivity to ramipril treatment; however, unlike in men, the response to ACE inhibition in women was independent of the underlying genotype. Thus, among patients at high risk because of heavy proteinuria and/or uncontrolled hypertension, all women and DD genotype men gain the

greatest advantage from ramipril treatment, whereas men with hypertension or proteinuria with the ID or II genotype are virtually unaffected by ACE inhibitor therapy. Other clinical trials[38,39] have shown that patients with DD polymorphism have a higher antiproteinuric response to ACE inhibitors than those with ID or II genotype. However, in another study,[40] no antiproteinuric response was noted in patients with DD genotype and nondiabetic CRF. Thus, additional studies need to carefully evaluate the possibility of interactions between gender, I/D genotype, ACE inhibition and renal progression.

2.4.3 Safety of ACE Inhibitors

ACE-inhibitors are generally well tolerated, but in patients with impaired renal function a few adverse effects such as hyperkalaemia and acute GFR decline may be observed.

Hyperkalaemia is due to the fact that ACE inhibitors lower circulating angiotensin II and, consequently, the production of aldosterone, impairing potassium excretion which may be reduced in patients with CRD.

The other well known kidney-related adverse effect of ACE inhibitors is the development of acute renal failure in patients with significant bilateral renovascular disease, volume depletion or severe congestive heart failure. The use of ACE inhibitors in these conditions is contraindicated. Patients with hypertension, particularly if highly renin-dependent, often receive ACE inhibitors with a diuretic, and the marked fall in blood pressure and renal perfusion pressure may even cause acute renal failure, usually reversible after discontinuation of study drug and correction of the volume depletion. Thus, temporary withdrawal of diuretic therapy (for at least 24 hours) is recommended before the first dose of ACE inhibitor is administered in order to limit the risk of acute, symptomatic hypotension.

ACE inhibitors should always be started at lower doses and then progressively up-titrated according to tolerability and action on blood pressure and proteinuria. Close follow-up measurements of serum potassium and creatinine levels are recommended; an evaluation of these parameters should be made before starting ACE inhibitor therapy and repeated 7 days after the first administration and subsequent dose titrations. Monitoring of haematocrit is also advisable since long term ACE inhibition may occasionally worsen the anaemia of CRF. The slight increase in serum creatinine levels (<30%), which usually occurs early during ACE inhibitor therapy, reflects an haemodynamically mediated reduction in GFR that may be renoprotective in the long term; thus, this is not an indication to withdraw the drug.[41] In contrast, withdrawal of the ACE inhibitor is recommended in patients with a sustained hyperkalaemia (≥5.5 mEq/L), despite dietary potassium restriction, concomitant diuretic treatment and effective correction of metabolic acidosis.

Data from the REIN studies show that, if these guidelines are adhered to, ACE inhibitors are well tolerated and can be safely administered in patients with moderate and even severe renal insufficiency.

2.4.4 Maximising the Effect of ACE Inhibitors

A low-sodium diet (sodium intake <100 mol/day is recommended) and/or diuretic treatment are advisable to increase the antiproteinuric effect of ACE inhibitors by maximally activating the renin angiotensin system. The use of a non-potassium sparing diuretic has the additional advantage of limiting the risk of hyperkalaemia. Intensified blood pressure control[20] also enhances the antiproteinuric response to ACE inhibitors, whatever treatment is employed. Preliminary evidence is also available that the reduction in proteinuria correlates linearly with enhancing doses of ACE inhibitors, and this is not dependent on the level of blood pressure control.[71]

3. Future Therapeutic Options

In fact, ACE inhibition is the best therapy available for proteinuric progressive nephropathies; however, this approach alone is not always sufficient to normalise urinary proteins or to fully prevent renal damage and GFR decline.[21,22,29-33] Thus, other treatments may synergise with ACE inhibitors in further limiting protein traffic and/or

interfering with events which may lead to interstitial inflammation and structural damage.[42]

Multidrug approaches have to be targeted to:

- maximise the response to ACE inhibitors through low sodium diet and/or diuretics and intensified blood pressure control;
- amplify the antiproteinuric effect of ACE inhibitors by the concomitant use of diverse antiproteinuric drugs such as angiotensin II receptor antagonists (AII antagonists), non-dihydropyridine calcium antagonists and perhaps low doses of nonsteroidal anti-inflammatory drugs (NSAIDs);
- inactivate, for example by ET receptor antagonists, the most important vasoactive and inflammatory mediators which are up-regulated by proximal tubular protein overload; and enhance glomerular function through the administration of growth factors (fig. 3).

3.1 Angiotensin II Receptor Antagonists

Both in animals with various types of progressive renal diseases and in humans with diabetic and nondiabetic chronic nephropathies, AII antagonists had an antiproteinuric effect apparently me-

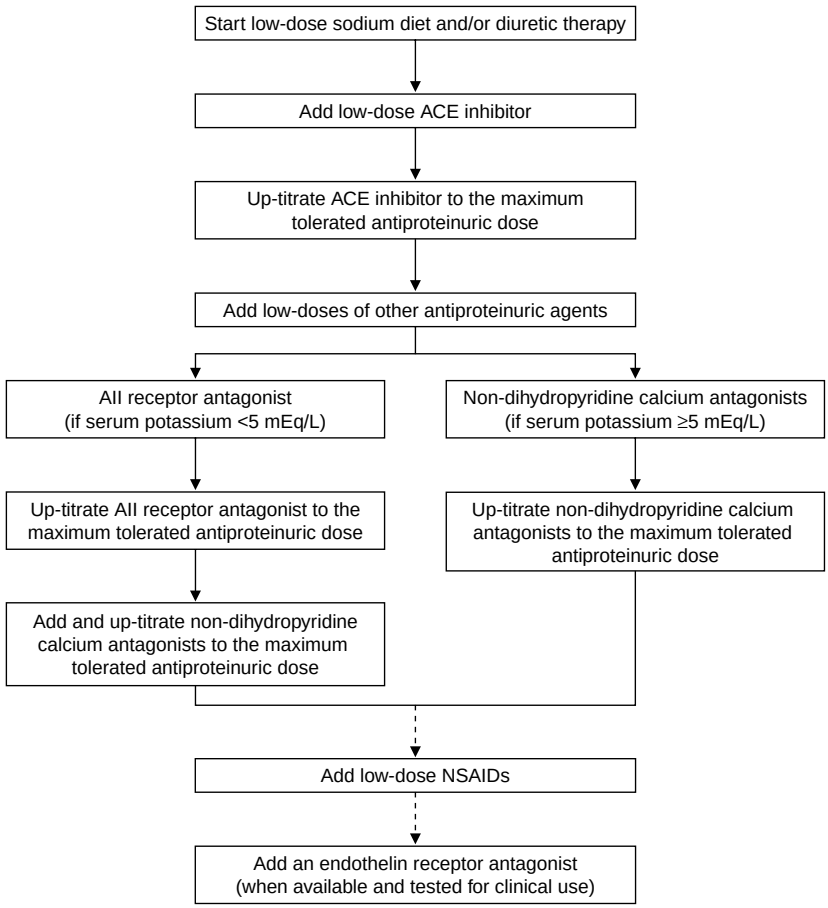

Fig. 3. A suggested algorithm to guide antiproteinuric treatment in patients with proteinuric chronic nephropathies. Withdraw diuretics for 24 hours before the first dose of ACE inhibitor is administered. Check serum potassium and creatinine levels within 7 days after any new treatment is started and any dose is up-titrated. **AII** = angiotensin II; **NSAIDs** = nonsteroidal anti-inflammatory drugs.

diated by a direct amelioration of glomerular barrier permselectivity.[43,44] In experimental studies of renal ablation, at comparable levels of blood pressure control, AII antagonists and ACE inhibitors were more effective than other antihypertensive drugs in reducing proteinuria.[45,46] Moreover, in rats with diabetic nephropathy, an ACE inhibitor and an AII antagonist were equally effective in preventing proteinuria, mesangial expansion and glomerular membrane thickening.[47] Also in humans, similar urinary protein excretion rate at comparable levels of blood pressure control were seen with AII antagonists and ACE inhibitors.[43]

We believe that by acting at two different levels (reduction of angiotensin II production and competition with AII receptors) the two compounds might synergistically inhibit AII activity and minimise the counter-regulatory responses of the system. This hypothesis is corroborated by experimental studies and short term studies with small numbers of patients in humans. In fact, in rats with renal ablation and with passive Heymann nephritis, the combination of AII antagonists and ACE inhibitors induced a greater renal protection than either treatment alone, and in 11 patients with chronic renal disease of various aetiologies, the addition of an AII antagonist to ACE therapy, induced a further 30% reduction in proteinuria and no change in creatinine clearance after 2 weeks of combined treatment.[48] Moreover, in 8 normotensive patients with IgA nephropathy, at comparable levels of blood pressure control, the combination of an AII antagonist and an ACE inhibitor decreased the urinary protein excretion rate more effectively than either agent given alone.[49]

These data are encouraging but need confirmation in larger numbers of patients evaluating the effects of the combination on safety parameters (namely serum potassium levels), renal haemodynamics and glomerular barrier size selectivity.

3.2 Non-Dihydropyridine Calcium Antagonists

Non-dihydropyridine calcium antagonists also have a specific antiproteinuric effect mediated by amelioration of glomerular barrier size selectivity.[50] In experimental diabetes mellitus, combined treatment with non-dihydropyridine calcium antagonists and ACE inhibitors reduced proteinuria and prevented mesangial matrix expansion and glomerulosclerosis more effectively than either treatment alone. Similarly, in patients with hypertension and type 2 diabetes mellitus with overt nephropathy, the calcium antagonist verapamil and the ACE inhibitor trandolapril in combination produced, at comparable levels of blood pressure control, greater reductions in proteinuria than higher doses of either agent alone.[51] These observations support the possibility that combined treatment with non-dihydropyridine calcium antagonists and ACE inhibitors may translate into slower progression of renal disease in the long term.

In contrast, dihydropyridine calcium antagonists, such as nifedipine and nitrendipine, have a variable effect on proteinuria ranging from an increase to a fall in urinary protein excretion.[52,53] This could be related to their different sites of action and different effects on intrarenal activity.[54] In fact, nifedipine causes preferential afferent arteriolar dilatation, allows more of the systemic pressure to be transmitted to the glomerulus and has no effect on glomerular barrier size selectivity in patients with chronic glomerulonephritis,[52] while nicardipine may decrease glomerular pressure by its prevalent efferent arteriolar dilatation.[53]

3.3 Nonsteroidal Anti-Inflammatory Agents

Many studies have documented the antiproteinuric effect of NSAIDs, in particular indomethacin, in chronic proteinuric nephropathies.[55-58]

In patients with nephropathy, indomethacin reduced proteinuria by improving intrinsic permselectivity of the injured glomerular capillary wall.[59] This effect is probably linked to the inhibition of thromboxane A2, an arachidonate metabolite which enhances urinary protein excretion when produced in excessive amounts at the glomerular level.[60] Of note, Perico et al.[43] found that combined treatment with indomethacin and enalapril (or irbesartan) decreased urinary protein excretion

rate and albumin fractional clearance more effectively than each individual treatment, without significant reductions in GFR and renal plasma flow.

These data were to some extent in contrast to previous studies showing acute renal function deterioration in nephrotic patients given ACE inhibitors and NSAIDs.[58,60] Evidence that in these series, but not in that by Perico et al.,[43] patients were recommended to follow a low-sodium diet, would suggest that fluid/sodium depletion may enhance the risk of NSAID renal toxicity.

Further studies are needed to better evaluate the risk/benefit profile of combined treatment with ACE inhibitors (or AII antagonists) and NSAIDs, before recommending this combination for long term treatment of patients with chronic renal disease.

3.4 Endothelin Antagonists

In experimental studies, selective ETA and ETB receptor antagonists reduced proteinuria and prolonged kidney survival despite poor blood pressure control.[61] Unselective endothelin receptor antagonists were even more effective and decreased blood pressure and proteinuria to the same extent as an ACE inhibitor.[62]

In a very recent study performed in rats with passive Heymann nephritis and heavy proteinuria,[63] combined treatment with an ACE inhibitor and an ET-1 antagonist reduced proteinuria more effectively and was more renoprotective than each drug alone. Thus, while ACE inhibitors may antagonise excessive protein trafficking through the glomerular filter, ET-1 antagonists would instead prevent the inflammatory reaction triggered by enhanced endothelin production by proximal tubuli as a consequence of abnormal protein overload.[64]

Whether combination with an ET antagonist may improve the antiproteinuric and renoprotective effect of ACE inhibitors in humans remains to be evaluated in the context of controlled clinical trials.

3.5 Growth Factors

Small clinical trials in humans have shown that the administration of insulin-like growth factor (IGF)-1, improved renal function for short period in both healthy volunteers[65] and patients with CRF.[66-69] Since its use is not without risk, including malignancies, a large multicentre study is required to define the role of IGF-1 in increasing renal function and delaying the need for dialysis.

Other factors, such as an osteogenic protein of the transforming growth factor-β group,[70] are currently being investigated in experimental models of progressive nephropathy.

4. Conclusions

Protein traffic is an important determinant of progression in chronic nephropathies and proteinuria is the best predictor of disease outcome. ACE inhibitors are the most effective intervention in patients with chronic nondiabetic proteinuric renal disease, reducing urinary protein excretion rate and slowing the progression to ESRF more significantly than other conventional antihypertensive agents. However, since this approach alone is not always sufficient to reduce proteinuria and to stabilise renal function and many factors are involved in the progressive renal injury secondary to glomerular barrier dysfunction and increased protein traffic, multidrug approaches should be used in patients with little or no response to ACE inhibitors. Thus, we hope that in future years a similar approach, through tight blood pressure control and the use of drugs targeting different levels of the sequence of events that eventually leads to renal scarring, will avoid ESRF even in most rapidly progressing nephropathies.

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