Prevention of progression and remission/regression strategies for chronic renal disease

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Abstract

Chronic renal disease (CRD) represents a major health problem, whose dimension is rapidly growing. Chronic nephropathies share common pathogenic mechanisms that contribute to renal disease progression, even independently of the original cause. Clinical studies found a significant correlation between the rate of GFR decline and both the blood pressure levels and the extent of urinary protein excretion. Antihypertensive drugs interfering with the renin-angiotensin system (RAS) decrease proteinuria and slow renal disease progression. However, the number of patients who reach end-stage renal failure despite RAS inhibitor therapy is still considerable and there is a great need to identify therapies that can arrest evolution of kidney damage. Outcome is remarkably improved when a multimodal strategy including dual RAS blockade, lipid-lowering agents, smoking cessation, and tight glucose control for diabetes is used. New drugs targeting specific determinants of progression might increase the fraction of CRD patients who reach disease remission.

Key words: proteinuric nephropathies, progression, remission, regression, ACE inhibitor, ARB, remission clinic.

Introduction

Chronic renal disease (CRD) represents a major threat to public health [1, 2]. A forecast analysis based on data from the US Renal Data System and Medicare predicts that by the year 2010 the total number of patients on renal replacement therapy will double and will exceed 650,000, which is expected to increase public expenditure for dialysis to $28 million per year [3]. Thus, halting the progression of chronic nephropathies to end stage renal disease (ESRD) is instrumental in substantially decreasing the need and cost for renal replacement therapy. This would be mostly important for developing countries, where facilities for dialysis are limited or altogether nonexistent and patients with CRD are facing an ominous fate.

A large number of experimental and clinical studies have demonstrated that chronic nephropathies share common pathogenic mechanisms that contribute to progression of renal failure, independently from the original cause [4]. In particular, clinical trials showed that both hypertension and urinary protein excretion rate are correlated with GFR decline in diabetic and non-diabetic CRD [4].

Drugs that interrupt the renin-angiotensin system (RAS), such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), represent effective antihypertensive agents with a spe-

cific antiproteinuric effect [4]. Reduction of proteinuria to normal range is however seldom achieved when these drugs are used alone and at the dosages recommended for BP control. Thus, use of maximal combined doses of RAS inhibitors, together with lowering of blood lipids, smoking cessation, and tight glucose control for diabetes, may increase the fraction of patients who have normalization of proteinuria and, possibly, remission or even regression of renal injury [5]. Moreover, during the last years new pathogenic mechanisms and potential therapeutic targets for chronic nephropathies have been identified, which may eventually further improve outcomes of patients with renal disease [6].

Determinants of chronic renal disease progression

Blood pressure

In animal models of chronic nephropathies, systemic hypertension is associated with increased intraglomerular pressure, an important determinant of renal disease progression [7, 8]. Accordingly, clinical trials showed that lowering blood pressure (BP) invariably retards renal disease progression [8]. Of major importance, ACE inhibitors and ARB are, among the antihypertensive drugs, the ones that most effectively lower intraglomerular capillary pressure [9]. In a seminal study, Mogensen *et al*. [10] reported that five patients with type 1 diabetes and a linear decline in renal function for several years had this tendency suddenly modified when antihypertensive treatment was initiated. This finding has subsequently been confirmed in many studies and similar observations have been reported in non-diabetic renal disease [11]. Hypertension, a hallmark of most chronic nephropathies, was thereafter recognized as a strong, independent risk factor for ESRD [12]. The Modification of Diet in Renal Disease (MDRD) study, which included patients with chronic renal failure, showed that those with the lowest BP also had lower progression of renal failure. In this study, among patients who had more than 1 g/day of proteinuria, those randomized to a mean arterial target of 92 mm Hg had a greater reduction in urinary protein excretion and a slower rate of GFR loss than patients who were randomized to a mean arterial pressure of 107 mm Hg [13].

Proteinuria

Glomerular hypertension in both diabetic and non-diabetic chronic nephropathies leads to increased glomerular permeability and excessive protein filtration. The ultrafiltered proteins are toxic to the tubular cells, resulting in tubular damage, interstitial inflammation, and scarring [14]. In experimental models of renal injury, the degree of proteinuria correlates with the magnitude of renal damage, and reducing proteinuria preserves renal function [8]. Proteins in the urine are normally absorbed by endocytosis in the proximal tubules. During periods of heavy proteinuria, the filtered albumin accumulates in lysosomes in the proximal tubular cells, causing cell disruption and injury. Other proteins, including ultrafiltered transferrin and immunoglobulin, and the intrarenal complement pathway exert an additional injurious effect that eventually results in glomerulosclerosis, tubulointerstitial fibrosis, and renal function decline [15].

Clinical studies found a significant correlation between the extent of urinary protein excretion and the rate of GFR decline both in diabetic [16] and non-diabetic [17] chronic nephropathies. Moreover, a large body of evidence has shown that whenever proteinuria is decreased, progression to ESRD is consistently reduced. The MDRD study found that a reduction of proteinuria, independent of the reduction in BP, was associated with a decrease in GFR decline and that the degree of protection of renal function achieved by lowering BP was dependent on the level of initial proteinuria [13]. Consistently, the Ramipril Efficacy In Nephropathy (REIN) study, including patients with non-diabetic chronic nephropathies, also found that a rapid and sustained reduction in proteinuria prevented or limited long-term GFR decline [18]. Finding that the extent of residual proteinuria was also a major determinant of disease progression provided further evidence of the pathogenic role of protein traffic [19].

This background prompted the definition of a "proteinuria hypothesis" that consists of three postulates: i) higher levels of proteinuria predict adverse clinical outcomes, ii) reduction of proteinuria correlates with slowing of renal progression, and iii) proteinuria is a surrogate end point and target of clinical interventions [20].

Slowing renal disease progression through renin-angiotensin system blockade

Before 1995, several small randomized trials of ACE inhibitors in patients with non-diabetic renal disease were reported [21-23]. These studies, however, reported conflicting results. Possible sources of variability included different methods of measuring renal function, different causes and severity of renal disease, use of different ACE inhibitors, and small sample sizes [24].

Then, the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) study, a large-scale trial of patients with non-diabetic renal disease, provided evidence of a slower increase in serum creatinine on ACE inhibition therapy [25]. These results, however, were flawed due to lack of data on hard end-points such as dialysis or transplantation and did not allow the conclusion

of whether the effect on this surrogate end point reflected a true renal protective effect. Moreover, a much more effective BP reduction on ACE inhibitors did not allow the establishment of whether this effect was specific for ACE inhibitors or merely reflected better control of arterial hypertension [24]. Conversely, the REIN trial compared ACE inhibitor and non-RAS inhibitor therapy on hard end-points, with the same target BP levels. In this study, patients who had more than 3 g/day of proteinuria and were treated with the ACE inhibitor showed a significantly lower rate of decline in GFR and a reduced risk for doubling serum creatinine or end-stage renal failure as compared with patients who received conventional therapy [18]. Moreover, 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 ESRD clearly indicated that renoprotection is linked to reduction of protein traffic [26]. After approximately 36 months of ramipril therapy, no additional patients progressed to the point of requiring dialysis, whereas patients who switched from conventional therapy to ramipril continued to develop ESRD [27].

A step forward: the Remission Clinic approach

The above evidence shows that ACE inhibitors and ARB are particularly effective in lowering urinary protein excretion, but reduction of proteinuria to normal range is seldom achieved when these drugs are used alone and at the dosages recommended for BP control. Thus, it has been hypothesized that higher dosages may have a superior antiproteinuric effect that is further enhanced by a low-sodium diet and the addition of a diuretic [28, 29]. Moreover, ACE inhibitors and ARB have an (at least) additive effect on urinary proteins, and the two drugs in combination reduce urinary protein excretion more effectively than single RAS blockade by each agent alone, even without further BP decrease [30]. Importantly, data also support the notion that hydroxymethylglutaryl CoA inhibitors (statins) may reduce proteinuria regardless of their effect on serum lipids [31]. Considering the different therapeutic targets and potential synergism among various drugs, a multimodal intervention strategy using all available tools to target urinary proteins seems a rational approach to maximizing renoprotection in patients with CRD [32]. Experimental data support this notion [33]. Indeed, in uninephrectomized passive Heymann nephritis rats, a model of severe proteinuria, combined therapy with ACE inhibitor, ARB, and statin almost normalized renal histology and function, which was not possible with either treatment alone (Figure 1) [33]. This approach, together with smoking cessation and optimal metabolic control in diabetics, has been formalized in an intervention protocol, the "Remission Clinic" programme (Figure 2), that has been applied in the day-to-day outpatient clinical activity to a cohort of 56 consecutive patients with chronic renal disease and heavy proteinuria despite ACE inhibitor therapy. Their outcome has been compared with that of 56 historical reference patients on conventional therapy titrated to BP, in the setting of a matched-cohort study [5].

The Remission Clinic programme significantly slowed GFR decline and reduced the risk for ESRD by 8.5-fold as compared with the conventional regimen. During the 7-year observation period, only

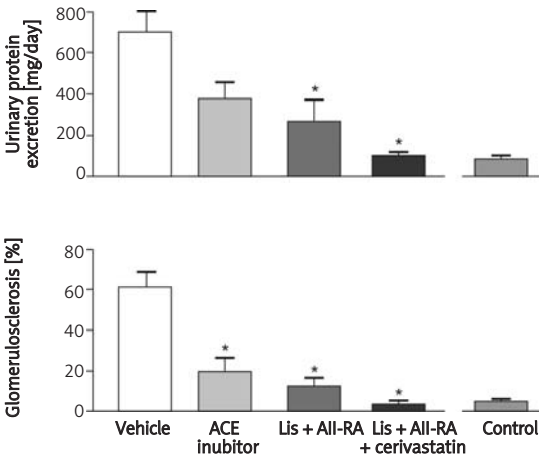
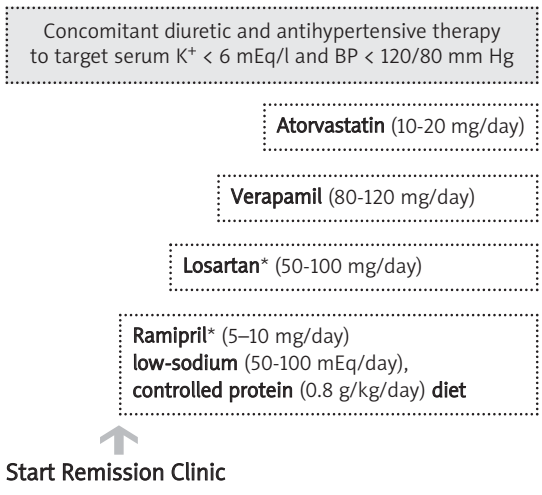


Figure 1. Urinary protein excretion and glomerulosclerosis evaluated at month 2 in PHN and control rats and at month 10 in PHN rats given vehicle, cerivastatin, ACE inhibitor, ACE inhibitor plus ARB, ACE inhibitor plus ARB plus cerivastatin, and in control rats
*$p < 0.01$ vs. vehicle [33]



Up-titration and combined therapy if serum $K^+ < 6$ mEq/l

Figure 2. Algorithm describing the key steps of the Remission Clinic intervention protocol [5]

two patients who were treated according to the Remission Clinic protocol progressed to ESRD, compared with 17 reference patients who were receiving conventional therapy. The Remission Clinic approach was also associated with more effective BP, serum cholesterol, and urinary protein reduction compared with conventional therapy. Serum potassium was similar in the two cohorts, and no patient withdrew from the Remission Clinic because of refractory hyperkalaemia or other serious adverse events [5]. Thus, the Remission Clinic approach can normalize heavy proteinuria, even in cases resistant to standard therapy, and reduction of proteinuria to normal range translates into stabilization of kidney function and effective prevention of ESRD. Notably, in patients whose proteinuria was lowered to less than 0.3 g/day, improvement of renal function was reported, which provided the proof of the concept that remission of kidney disease is a feasible target in day-to-day clinical practice.

This evidence prompted the institution of a network of Italian Nephrology Centres applying the Remission Clinic approach in the outpatient clinical activity. Patients' data will be centralized by using a unified on-line database that will allow assessment, on a large scale, of the effect of this therapeutic strategy on the outcome of patients with chronic proteinuric nephropathies. This project will be coordinated by the Clinical Research Centre for rare diseases Aldo e Cele Dacco', Ranica (BG), Italy (http://clinicalweb.marionegri.it/remission).

New perspectives for remission/regression of chronic renal disease

Over the last years, research has been focusing on new targets to further reduce proteinuria and possibly improve outcomes of chronic nephropathies. Many molecules have been successfully tested in experimental models of renal disease, with different protective effects on kidney function and structure. Aldosterone antagonists and the renin inhibitor aliskiren are, among them, the ones that provided the most convincing results.

Aldosterone antagonists

A growing body of experimental and clinical evidence suggests that aldosterone may act as an independent and powerful mediator of renal damage. Moreover, attenuation of growth-promoting and other fibroproliferative effects of aldosterone protects against progressive renal injury [34].

In different models of kidney injury, spironolactone – a non-selective aldosterone receptor antagonist – limited the development of glomerulosclerosis and tubulointerstitial fibrosis [34]. Similarly, in Dahl salt-sensitive rats, a model of hypertensive glomerulosclerosis, eplerenone – a non-selective aldosterone receptor antagonist – prevented podocyte damage, proteinuria, and glomerulosclerosis [35]. The renoprotective effects of spironolactone potentiate when rats are given the aldosterone receptor antagonist in combination with an ARB [34]. These experimental findings may have important clinical implications, because blockade of the aldosterone receptor is instrumental in protecting the kidney from further damage even in the presence of angiotensin receptor antagonism. Importantly, small studies consistently showed reduction of albuminuria or proteinuria in diabetic patients with overt nephropathy receiving aldosterone antagonists either alone or as add-on therapy to RAS blockers [36, 37]. Even in patients who had non-diabetic CRD and were already treated with ACE inhibitors and/or ARB, spironolactone effectively reduced proteinuria [38]. Whether sequential blockade of RAS with ACE inhibitors or ARB and aldosterone antagonists provides additional long-term benefits to patients with chronic nephropathies is still however unknown. As hyperkalaemia represents a major concern of anti-aldosterone therapy, prospective, randomized trials are necessary to confirm the efficacy and safety of aldosterone receptor antagonism on the progression of CRD.

Aliskiren

A reactive increase in the activity of renin, widely considered the rate-limiting component of the RAS, occurs when either ACE inhibitors or ARB are used for long periods [39]. Hence, inhibiting renin itself has been an important, although until recently elusive, goal. Thus, the recent introduction of aliskiren, an oral renin inhibitor, represents an important landmark in the history of RAS blockade [39].

Studies to date indicate that aliskiren is an effective, once-a-day antihypertensive agent which reduces BP by approximately the same extent as most commonly used drugs. Recently, Parving *et al*. [40] reported the results of the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study. This was a double-blind, randomized, placebo-controlled trial in which type 2 diabetic patients with hypertension and proteinuria who were already receiving losartan were randomly assigned to receive aliskiren or placebo. After 6 months of therapy, aliskiren reduced the urinary albumin/creatinine ratio by 20% as compared with placebo, despite similar blood pressure control.

This encouraging result prompted the design of new randomized, controlled trials with hard end-points and longer follow-up, to assess whether aliskiren may really provide further renoprotection over ACE inhibitors or ARB alone. Among them, the ALTITUDE study (NCT00549757) is an ongoing trial enrolling 8,600 diabetic patients with protein-

uria and history of cardiovascular disease. Patients receiving background treatment with an ACE inhibitor or an ARB will be randomized to add-on therapy with aliskiren or placebo. The primary composite end-point will include both renal and cardiovascular events [41].

However, optimal therapy of proteinuric chronic nephropathies is based on dual RAS blockade with ACE inhibitors and ARBs [5]. Aliskiren-based therapeutic regimens should be compared to dual RAS blockade with ACE inhibitors or ARBs with the aim of providing evidence of superior renoprotective effect or reduced risk of hyperkalaemia. Another intriguing issue might be to assess whether triple RAS blockade with ACE inhibitor, ARB, and aliskiren is more effective than dual RAS inhibition in retarding renal disease progression. This information is essential to establish whether aliskiren has a specific renoprotective effect that may help further improve the outcome of patients with progressive nephropathies without unnecessarily increasing treatment costs. In the meantime ACE inhibitors and ARBs, either alone or in combination, should still be considered the first-line therapy for patients with chronic proteinuric renal disease.

Conclusions

ACE inhibitors and ARB reduce proteinuria and preserve renal function in patients with CRD. A multimodal strategy targeted to proteinuria reduction through combined use of maximal doses of these drugs, in addition to statins, smoking habit cessation and optimal glycaemic control, seems to further improve outcomes of those patients with residual proteinuria despite maximal ACE inhibitor or ARB therapy.

Aldosterone antagonists and aliskiren exert an antiproteinuric effect by blocking RAS in two different sites. Future studies will clarify whether they may offer additional renoprotection when combined with ACE inhibitors and ARB.

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