REVIEW ARTICLE

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Non immunological therapy in nephropathies leading to chronic kidney disease and post transplant CKD

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INTRODUCTION

The western world, while experiencing a general aging of the population, is also facing a significant increase in prevalence of chronic kidney disease, a situation which has been defined as pandemic.

The high mortality and comorbidity, especially in terms of cardiovascular disease, have led to a significant increase in hospitalisation with a great rise in public health costs, setting a trend which will become unsustainable over the next few decades, even in the most developed countries.

These epidemiological data have underlined the need for prevention campaigns and have prompted researchers and clinicians to develop new, more specific treatments able to slow down the progression of chronic kidney disease towards dialysis. A deeper understanding of the pathogenetic mechanisms of nephropathy progression is sorely needed to obtain these results.

Once sclerosis is established and the initial pathogenetic noxa has been extinguished, the sclerotic progression of different nephropathies follows a standard path, despite the initial cause.

Finding a therapy effective under such conditions, in native kidneys as well as in transplanted organs, is the challenge the third millennium poses for nephrologists.

In this review we firstly describe the main risk factors and pathogenetic mechanisms involved in nephropathy progression, and then the results obtained with drugs which basic research has identified as potentially useful in experimental animal models as well as in rigorous clinical trials.

PATHOGENESIS AND PROGRESSION

Role of nephronic mass reduction

The observation that renal disease progresses toward chronic renal failure even when the initial noxa has been removed is accepted nowadays and it has been useful in aiding understanding that the loss of a critical mass of glomeruli *per se* plays a

key role in triggering pathogenetic mechanisms leading to progressive loss of the remaining functional nephrons. This hypothesis is strongly sustained by the experimental models of the 5/6 nephrectomy[1-3]: in the remaining sixth part of the kidney, the initially histologically normal glomeruli show sclerotic lesions similar to those of focal segmental glomerulosclerosis (FSGS) and rats develop hypertension, proteinuria and chronic kidney disease[4].

The ancestral hypothesis suggested by Brenner underlined the central role of glomerular hyperfiltration, with increased filtration rate related to the relatively greater vasodilatation of afferent as compared to efferent arteriola[5,6]. The event triggering the subsequent glomerular hypertension, appearance of proteinuria and progressive sclerosis leads to loss of renal function. The relative vasoconstriction of the efferent arteriola is the consequence of the increased production of Angiotensin II; thus, a blockade of the RAS system with angiotensin-converting-enzyme inhibitors (ACE-I) or the use of receptorial antagonists (ARBS), leading to a vasodilatation of the afferent arteriola, and the fall of the filtration rate[5,6]. This hypothesis has been confirmed in animal models of streptozotocine-induced diabetes which induce glomerular hyperfiltration, glomerular hypertension and a shielding effect of a blockade of the RAS system with angiotensin-converting-enzyme inhibitors (ACE-I) or the use of receptorial antagonists (ARB) in the appearance of proteinuria and glomerular sclerosis.

The remnant nephrons after 5/6 nephrectomy or after critical reduction of renal mass are characterised by an altered synthesis of growth factors[8-13]. Both hypotheses, haemodynamic and hypertrophic, suggest a key role for Angiotensin II. An increase in the synthesis of Angiotensin II can activate a series of different intracellular signalling pathways which lead to growth factor transcription and translation responsible for the hypertrophy, mediated by the synthesis and activation of cyclines involved in cellular duplication. Ang II is also responsible for the synthesis of prosclerotic collagens and enzyme as inhibitors of metalloproteases, involved in the normal turnover of the interstitial matrix. This leads to proteinuria and enhanced activity or synthesis of profibrotic/hypertrophic factors such as TGF-β and PAI-1[8-13].

Activation of the RAS system has an independent effect from systemic blood pressure[14-17]. Only severe hypertension, with values able to alter the mechanisms of autoregulation of renal blood flow, can induce endothelial glomerular damage and subsequent ischemic/sclerotic lesions. If renal autoregulation is impaired, as it is in the remnant kidney, even moderate elevation of systemic blood pressure can induce significant alteration of intracapillary pressure responsible for the phenomenon of shear stress and glomerular damage[18-21]. Experimental evidence has shown that the histological aspects in the remnant nephrons are similar to those seen in focal segmental glomerular sclerosis (FSGS) in the absence of endothelial lesions due to malignant hypertension. In any case, a strict control of blood pressure is mandatory to slow down the sclerotic evolution of different nephropathies, and this is particularly true for those with a critical reduction of the nephronic mass, able to impair the renal blood aurotegulatory systems. The latest guidelines for CKD treatment underline the importance of an aggressive approach to hypertension, establishing targets of 125-130/85 mmHg for systemic blood pressure values. This is even more important in the proteinuric forms of nephropathies. In the meantime, it is essential to avoid overtreatment, and systolic blood pressure values, especially in the elderly, should not fall under 110 mmHg.

The correlation between increased glomerular filtration pressure – and consequently shear stress on the capillary walls – and the sclerotic progression of kidney diseases is suggested by the structural features of the glomerular filtration barrier. This is a complex system involving three different structures: the fenestrated glomerular endothelium, the basement membrane and podocytes. The slit diaphragm, as described by Karnosky thirty years ago, is only the very last obstacle to plasma protein passage.

In this scenario, the podocyte plays a pivotal role in structure and function of the glomerular filtration barrier. It leads the embryological development and trophism of endothelial cells through VEGF production and synthesises components of the basement membrane (GMB). These latter include anchorage proteins, such as integrins, and integrin-like proteins, and proteins which make up the complex network of the slit diaphragm including, among others podocyn, nephrin and CD2Ap. Podocytes, as well as endothelial cells, are not only activated by immunological stimuli, but also by modifications in haemo-

dynamic forces caused by shear stress, as described in cases of nephronic mass reduction.

This important loss of functioning nephrons activates intracellular signalling pathways with consequent alteration of the endothelium and podocytes. The cells lose their mature phenotype, change the three-dimensional organisation of their cytoskeleton proteins and of the slit diaphragm and lose anchors to the GMB. Often, this process ends in apoptosis of podocytes – with podocytopaenia and podocyturia – leaving areas of the GMB completely naked. These modifications are responsible for alteration of glomerular filtration with passage of plasma proteins into the Bowman's space. These structural changes lead to abnormal intratubular protein trafficking, exceeding the physiological tubular reabsorption capacity, and ending in proteinuria.

Moreover, unusual presence of proteins in the Bowman's space induces the activation of epithelial cells which start to proliferate, progressively filling the usually empty space. Consequent ischaemic collapse of capillary walls, glomerular sclerosis and progressive nephrons loss will lead to end stage renal disease (ESRD) and dialysis.

Abnormal intratubular protein trafficking starts, a vicious circle which hastens glomerular sclerotic evolution, activating tubular cells and inducing production and release of chemokines responsible for interstitial monocyte infiltration with enhancement of the damage.

Podocytes – which normally lose their duplicative skills once the mature phenotype is acquired – can de-differentiate under the influences of these mechanisms and regain cellular replication skills and induce endothelial cell regeneration via the synthesis and release of VEGF–neo-angiogentic factor. Thus, even if it is impossible to have new glomeruli formed after birth, the persistence of undamaged areas in the glomeruli, with preserved capillary walls tree, in partial sclerotic glomeruli can lead to restoration of the glomerular architecture through a complex action in which podocytes play a pivotal role[22].

Role of the Renin-Angiotensin-Aldosterone system (RAS) in renal damage progression.

The importance of the RAS system in the "non immunological" progression of nephropathies has been suggested by the extreme efficacy of its inhibitors in slowing progression to ESRD, both in experimental models and in clinical trials. RAS system inhibitors such as ACE-I reduce hydraulic intracapillary pressure secondary to the vasodilatation of the afferent arteriola. This effect results from a double inhibitor mechanism, first the synthesis of Angiotensin II and second by inhibiting chimase then degradation of bradikinine. On the other hand, type 1 receptor inhibitors (ARB) do not affect the bradikinine and are thus less effective in inducing the dilatation of afferent arteriola and so diminishing hydraulic intracapillary pressure. The ACE-I/ARB association has a synergic effect in slowing down sclerotic progression toward ESRD both in experimental models and clinical trials[23-25].

Commercially available ARB are specific to the type-1-angiotensin II receptor (ATI) and have no effect on the type 2 receptors (ATII). ATII receptors contrast some of the effect mediated by ATI receptors, are less effective in inducing vasodilatation, inhibit cellular duplication and promote induction of apoptotic mechanisms[26-29]. Apoptosis is often associated to minor damage as compared to necrosis. In fact, apoptotic cells are removed without the activation of prosclerotic cytokines and chemokines. The lack of ATII, drug-induced or genetically determined, is associated with a diminished apoptosis in response to fibrotic stimuli[31,32].

Theoretically, combined therapy with ACE-I and ARBS could have some advantages, blocking ATI action and maintaining ATII activity[33]. Nevertheless, in experimental models, the combined use of ACE-I and ARB has not shown additive effects in slowing down sclerotic progression in nephropathies as compared to the use of ACE-I alone, even when achieving a similar control of blood pressure values[34,35]. In transgenic mice hyperexpressing ATII receptors, sclerotic damage after 5/6 nephrectomy is less important than in wild animals[36]. Evidence from clinical trials, even though conducted on a small number of patients, has confirmed that combined use of ACE-I and ARB has a synergic effect on reducing proteinuria, which is not dependant on blood pressure control[37,38]. In a trial studying diabetics, in hypertensive patients the combined action of ACE-I and ARBS has been able to significantly reduce blood pressure and albuminuria as compared to ACE-I alone[39].

At the moment we lack studies comparing high dose combined therapy (ACE-I/ARB) and use of ACEI alone. This combined therapy has been shown, in small clinical trials, to have no important side effects[40].

Different mechanisms can explain the better results obtained with combined therapy compared to the single blockade of the RAS system. One is the antifibrotic effects, probably due to the enhanced synthesis of bradikinine and the other the action of ATII, as shown in recent studies into the urinary excretion of transforming growth factor (TGF)-β[41].

The potential better effect of combined therapy could be due to the almost complete abolishing of Angiotensin II production and the inhibition of the action of the lower amount of Angiotensin II still produced in ATI receptors. In experimental models, it has been demonstrated that even at a dose which is higher than those used for human therapies, ACE-I are unable to completely inhibit the RAS system[42], and clinical trials with patients undergoing ACE-I therapy for long periods showed a residual persistent activity of the RAS system, suggesting the existence of an independent Angiotensin II production pathway, probably related to chimotripsin-like enzymes.

All these observations have led researchers to develop direct renin antagonists. Renin can have a direct effect on kidney function, not mediated by the RAS system, mediated by specific receptors on mesangial cells[43].

The role of the RAS system and Angiotensin II on sclerotic progression of nephropathies is not limited to haemodynamic effects on the afferent arteriola. Indeed, Angiotensin II in a receptor-mediated manner can activate intracellular signalling pathways, such as NF-kB and AP-1. This leads to regulation of the cell cycle by an action on cyclin activity, to transcription of sclerogenic growth factors and genes encoding regulatory molecules for enzymes involved in the normal turnover of the interstitial matrix, such as PAI1[44-46].

In fact, ACE-I and ARBS in experimental models modulate the fibrosis regression mechanisms, through the delicate balance between synthesis and degradation of extracellular matrix (ECM).

Finally, Angiotensin II induces hypertrophy and hyperplasia of smooth muscle cells in the blood vessels and of mesangial cells[47,48]. Monocytes-macrophages, involved in nephropathies evolution, are provided with RAS system enzymes and respond to ACE-I and ARB.

Role of aldosterone

Blocking the RAS system through haemodynamic and non haemodynamic mechanisms induces not only an antiproteinuric effect, but reduces the velocity of sclerotic progression toward ESRD and even to a regression of sclerotic lesions with restoration of the normal glomerular function and architecture.

Over the past few years, fresh attention has been paid to the final product of RAS system activation: aldosterone. Aldosterone has been identified as a potential major protagonist in both chronic heart and kidney diseases[49] and it is now hypothesised that the deleterious effects of RAS system activation are related to aldosterone and that the beneficial effects of ACE-I could be greatly dependent on aldosterone's reduced synthesis and activity[34].

Prolonged aldosterone administration in mice leads to myocardic fibrosis and left ventricular hypertrophy[34], and aldosterone infusion reduces the positive protective effects of ACE-I and ARB on kidneys in hypertensive mice and in mice with 5/6 nephrectomy[50-52]. Spironolactone, an aldosterone antagonist, has been shown to reduce arteriolopathies and interstitial fibrosis in experimental models of cyclosporin-induced chronic toxicity and in attinic nephropaties, its effects apparently mediated by the inhibition of PAI-1 synthesis[54].

Angiotensin II directly stimulates PAI-1 synthesis via the AT-I receptor, independent of TGF-β neo-transcription. Moreover, aldosterone can interact with Angiotensin II, enhancing PAI-1 synthesis[54]. These data suggest that aldosterone's negative effect on the kidney is greatly due to regulation of PAI-1 synthesis[54].

Aldosterone modulates vascular tone, probably enhancing the vasocostrictive action of catecholamine, altering vasodilatatory response to acetylcholine and enhancing Angiotensin II receptor expression[55].

Aldosterone's prosclerotic activity, both expressed directly and via transcriptional regulatory activities, is independent of its sodium dependent regulation of blood pressure[57]. Aldosterone infusion in normal mice and single kidney mice enhances renal transcription of TGF-β mRNA, ACE, and AT1R.

The blockade of aldosterone prevents these deleterious effects and in clinical trials spironolactone in association with ACE-I and ARB enhances their antiproteinuric effects[58-60]. However, the risk of hyperkalaemia limits the use of aldosterone blockers together with ACE-I and ARB.

Role of proteinuria in sclerotic progression of nephropathies

Experimental and clinical evidence suggests that ultrafiltrated plasma proteins in Bowman's space may play a central role in the sclerotic progression of nephropathies.

Proteinuria is actually considered a marker of glomerular damage and responsible for sclerotic evolution through induction and perpetuation of inflammatory lesions[61]. Exposition of tubular cells on their apical side to such proteins as albumin, IgG and transferrin induces synthesis of vasoconstrictive factors, such as endothelin-1 (ET-1), growth factors responsible for renal tissue damage progression through induction of cellular proliferation. Moreover, matrix synthesis and production of chemoattractive molecules such as MCP-1, RANTES and IL-8, are stimulated[62-64]. Protein overload in tubular cells determines also neoexpression of fractalkine, which promotes mononucleated cell adhesion to tubular cells via CX3CR1 receptors[65]. Anti-CX3CR1 antibodies limit adhesion of monocyte-macrophagic cells to tubular cells. Proteinuria can activate nuclear translocation of nuclear transcription factor NF-kB, able to control sclerogenic, inflammatory and chemoattractant genes. The abnormal intratubular proteinuin trafficking tubular is probably able to induce oxygen peroxide via the activation of protein kinase C (PKC), as an answer to proteic tubular overload. This would be the main mechanism, even if a similar role may be played by MAP, and in particular by its isoform p38, and by other stress signalling pathways[66].

Epithelial proximal tubular cells express receptors for Ig and complement components and their activation leads to an oxidative burst able to activate chemoattractive molecules. Moreover, epithelial proximal tubular cells are able to produce C3.

Role of interstitial infiltrate

Interstitial infiltrate is considered a marker of the entity of glomerular damage and is responsible for ischaemic effects on remnant nephrons. A diminished capillary density in the interstitium, as has been observed in chronic kidney diseases, is probably responsible for sclerotic progression of nephropathies. It is not yet clear if the low number of such vessels is cause or consequence of sclerotic progression of nephropathies ending in ESRD.

Cells infiltrating renal interstitium are a source of sclerogenic cytokines and vasconstrictive factors. Therapeutical approaches designed to reduce inflammatory cell infiltration have had a positive effect on slowing down the sclerotic progression of renal diseases. In experimental models of urinary tract obstruction, ACE-I reduce inflammatory infiltrate entity and fibrosis. In human diabetic nephropathy the interstitial infiltrate precedes collagen accumulation and glomerular filtration rate reduction.

Infiltrating cells may be myofibroblasts, able to produce collagen, expressing smooth muscle alpha actin (SMA), a marker of miofibroblatic cells in experimental models as well as in human pathology.

It has been proposed that these cells have a bone marrow origin, but the major opinion nowadays is that they result from a phenotypical transformation of normal epithelial tubular cells which have a mesenchimal origin.

Damaged tubular cells may alter their phenotype both *in vitro* and *in vivo*, by initially expressing the fibroblastic specific protein (FSP-1), then migrate in the interstitium and assume miofibroblastic features. This mechanism could be regulated by the surrounding matrix, altered by proteolitic processes which, with the cooperation of growth factors such as insulin like growth factor II, integrin-linked kinases, EGF, FGF-2 and TGF-β, could initiate the phenotypical transforma-

tion. Factors inhibiting epithelial-mesenchimal transformation, such as the hepatocyte growth factor and the bone morphogenetic factor-7 (BMP-7), have been discovered and used in order to inhibit fibrosis in experimental models of different chronic kidney diseases.

Dyslipidemia

Patients with CKD often have dyslipidemia. This is particularly true for those patients with a high degree of proteinuria. This metabolic alteration negatively affects not only the rate of nephropathy progression but also significantly increases morbidity and mortality risks of cardiovascular diseases in these patients. Both mesangial and endothelial cells express receptors specific for LDL and for oxided LDL (LDLox): these receptors are called LOX. LOX activation induces an oxidative burst and transcriptional activation of NF-kB. The important role played by lipids is confirmed by the presence of sclerotic lesions in rare familiar disease such as lecitin-cholesterol acethiltransferase deficiency and apolipoprotein E deficiency.

Therapeutical approaches and life style changes in sclerotic progression rate of nephropathies and post transplant CKD

Since the beginning of the '90s the Bergamo group has shown that sclerotic progression rate of nephropathies, independent of the initial pathogenesis, is strictly related to the entity of proteinuria and that this deleterious effect is amplified by high blood pressure[67]. Recently the AASK study has provided evidence that even lower levels of proteinuria enhance the relative risk of developing ESRD and cardiovascular diseases. Many different approaches have been tried in order to limit tubular protein load and subsequently reduce the velocity of sclerotic progression of CKD. Jafar has introduced the key concept of "current proteinuria," meaning the proteinuria still present after specific treatment has been given for different nephropathies. Part of the Jafar hypothesis is that the

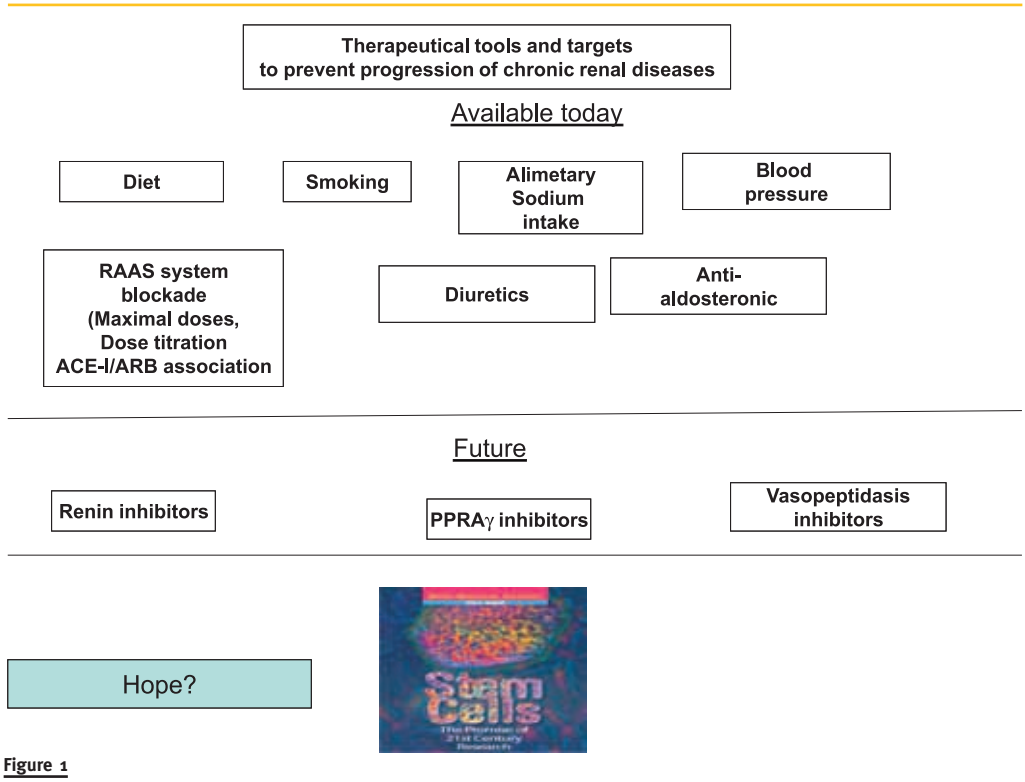

Figure 1

current proteinuria which leads the disease progression and the cut-off value could be established at a rate of proteinuria/creatininuria >0.5mg/mg.

This begs the question as to which tools, pharmacological or otherwise, can help us to contain the current proteinuria and slow the progression of nephropathies. Different approaches have been suggested, and their application in different studies has had encouraging results.

We will briefly discuss therapeutic strategies, pharmacological and otherwise, and their results. Key factors greatly involved are body weight and calorie control, smoking, sodium intake, diuretics, RAS system blockade and future possible therapeutic tools (Fig. 1).

Excessive body weight, with a BMI >27-29, negatively influences not only CKD progression rate, but also significantly increases cardiovascular risk in nephropathic patients.

Zuckerman mice are a spontaneously hypertensive mice which develop proteinuria and CKD early in their life. In this experimental model it has been underlined that body weight directly influences glomerular filtration rate, with hyperfiltration and RAS system activation; moreover fat tissue is involved in the developing of both proteinuria and sclerosis by means of leptin, whose synthesis is mediated by cytokines and TGF-β. These data have been recently confirmed by Praga (2006)[70]. Morales[71] in 2003 produced evidence of the positive effect of body weight loss on proteinuria levels in patients with chronic kidney disease and that, *vice-versa*, a direct relation exists between body weight and proteinuria entity. A 5% reduction of body weight was associated to a reduction of up to 3% in proteinuria levels. Partially related to obesity, the direct relationship between protein income and rate of renal function loss is well known, as shown in 2001 by Giordano[72]. This idea was re-elaborated in 2007 by Palmer, suggesting a protein income of 0.8g/day in proteinuric CKD patients[73].

Together with dietary habits, other behavioural attitudes play an important role in modifying proteinuria levels and CDK progression rate. Among these is smoking. Briganti *et al.* (2002) clearly showed that smoking significantly increased both GFR rate loss and proteinuria/creatininuria rate in a population of diabetic patients treated with ACE-I[74]. These data were confirmed by a screening in the Gubbio study[75].

Sodium intake is the other dietetic factor with an influence on proteinuria levels and CDK progression rate. In a randomised controlled clinical trial involving Afro-American patients, Swift showed that a moderate reduction of sodium intake would lead to a significant reduction of both blood pressure and proteinuria levels in hypertensive subjects. A reduction of 169-189 mmol/day of sodium intake was associated with a 30% reduction in proteinuria levels[76]. Sodium intake leads us to another important factor that needs to be controlled in order to prevent or slow down sclerotic progression of renal damage and reduce proteinuria: hypertension. Up-to-date guidelines (2007, Journal of Hypertension) suggest that blood pressure should be below 130/80 mmHg in diabetic patients with CKD, maintaining systolic values over 110 mmHg. Contradictory results have, however, emerged. Ruggenenti randomised patients with non diabetic CKD into two groups (intensified blood pressure control *versus* standard therapy) using ACE-I for a 54-month follow-up. No significant differences were observed in the two groups[77]; however, the small number of patients must be taken into consideration.

Hypertension, sodium intake, nephron mass loss, proteinuria, ischaemic tissue damage hyperuricaemia and reduced hydrossilated vitamin D synthesis are all factors involved in RAS system activation.

Fliser observed a significant reduction of CRP and serum levels of IL-6, TNF and MCP-1 in hypertensive patients with CRP >3mg/dl treated with ACE-I for 6 to 12 weeks[79].

It is clear, on the other hand, that the RAS system blockade has represented over the last two decades the potential key factor in reducing sclerotic progression rate of nephropathies. Experimental studies and clinical trials have proposed a step-by-step pharmacological approach for RAS-inhibiting drugs, to be used in sequence in order to reduce the kidney damaging effect of proteinuria. Different evidence-based studies and randomised double-blind, controlled clinical trials involving big populations suggest a therapeutic scheme that involves at the beginning

ACE-I or ARBs at antihypertensive dosages. When there is a very poor answer, it is possible to associate a diuretic, and even the ACE-I/ ARA II combination to maximum dosage.

At the beginning of the '90s our group demonstrated that IgAN patients' moderate proteinuria had a local activation of the RAS system[77].

A protective role of ACEI in reducing renal functional loss rate, thanks to control of proteinuria, was underlined more than ten years ago by Italian groups leaded by Giuseppe Remuzzi[80] and Giuseppe Maschio[81]. Their works showed that ACE-I (ramipril and benazepril) had a renoprotective effect in non diabetic dependent CKD patients, independent of proteinuria levels.

Similar data have been obtained in the GISEN trial, studying non diabetic patients with CKD and proteinuria ›3g/day treated with Ramipril *versus* placebo. After 24 and 42 weeks, the two groups showed significant differences in terms of proteinuria level reduction and organ survival[82]. Some years later Jafar confirmed these conclusions, using different drugs. The same author, in a meta-analysis of 11 studies, including 1260 patients with non diabetic nephropathy (AIPRD study) showed that ACE-I have an antiproteinuric effect which is independent of their antihypertensive action. Eliminating bias due to different blood pressure values and proteinuria, the risk of chronic renal disease progression was significantly lower in patients treated with ACE-I[83]. In addition to this protective effect on renal deficiency progression rate, ACE-I have proved themselves able to reduce cardiovascular mortality incidence in CKD patients, as shown in the HOPE study[84].

In diabetic nephropathies, the IDNT study involved 1590 patients, grouped into quartiles of systolic blood pressure values, treated with calcium channel blockers (amlodipine 10 mg/day), placebo or an ARB receptor blocker (irbesartan 300 mg/day) with a 2.6 year follow-up[85]. A significant reduction in relative risk of reaching the established end-point (doubling of serum creatinine levels or ESRD) has been observed. The same study has suggested that a better control of systemic blood pressure (target 120-130 mmHg) would positively influence renal outcome, while values lower than 120 mmHg could increase mortality[85].

A further study, by Barnett (2004), evaluated the nephroprotective effect of ACE-I and ARB in patients with diabetic nephropathy. In that study, 205 patients were treated with telmisartan 80 mg/day or enalapril 20 mg/day and followed for 5 years, with no significant differences seen in glomerular filtration rate loss. The Strippoli meta-analysis (2004) confirmed that both ACE-I and ARB have a protective effect on diabetic nephropathy, at different stages of the disease, in micro- and macro-albuminuric phases as well as in progression towards CKD and cardiovascular mortality[86].

With the only exception the Russo study in which IgA nephropathy patients were evaluated[37], there are no data supporting the idea of a better antiproteinuric effect of ACE-I using higher dosages of these drugs.

It is well known that diuretics enhance the effect of ACE-I. Hydrochlorotiazide combined with sodium intake restriction has shown an antiproteinuric effect[87]. While in diabetes-related nephropathies combination ACE-I and ARB therapy has shown no synergic effects, the COOPERATE study showed that treating non diabetic nephropatic patients with trandolapril plus losartan led to a significantly better reduction in proteinuria levels and in percentage of patients reaching the defined end-point after a 36-month follow-up[88]. Nakao, using trandolapril and losartan, showed that only 11% of patients involved in his study reached the end-point, compared to the 23% of patients treated with a single-drug therapy, either ACE-I or ARB[88].

These studies suggest a different therapeutic approach to proteinuric patients with nephropathies with different pathogenesis. In those with diabetes-related CKD, studies such as RENAAL and INDT have produced evidence that ibersartan has a renoprotective effect due to the RAS system blockade, with a significant reduction of sclerotic evolution rate. Results were not confirmed by the DETAIL study, though[89].

While many studies have focused on proteinuric nephropathies with renal failure on native kidney, very few data are available on patients with kidney transplantation with chronic transplant disease. In an experimental model of renal transplantation with chronic transplant nephropathy, (CAN) type I ARB,

but not type II, have been able to reduce CAN lesion severity, proteinuria levels and fibrosis and apoptosis percentages[90]. In a small number of patients with CAN, losartan has induced a significant reduction of PAI-1.

In a cross-over study in 18 transplanted patients, only losartan (50-100 mg/day) and not carvedilol (12.5-25 mg/day) was able to reduce excretion of such markers as CAN as NAG, TGF-β and type III pro collagen[91].

In a retrospective study involving 72 patients, 23 of which were treated after renal transplantation with RAS system blockade, multivariate analysis of serum creatinine during the first year after the transplant, proteinuria, histological activity score and systolic blood pressure at the time of diagnostic biopsy has confirmed the central role of the RAS blockade in improving renal survival[92].

Recently, Henze evaluated patient and transplanted kidney survival in 2301 patients treated or not with RAS system blockers. RAS system blockade did not modify patient survival or organ survival but when death was considered as event, a significant difference in the transplanted organ survival for those patients treated with ACE-I or ARB was observed[93].

As previously discussed, aldosterone has recently gained major attention as a potential central factor in the pathogenesis of sclerotic nephropathies progression. The Fogo group showed, in an experimental model of attinic nephritis, that spironolactone is able to reduce both sclerosis index and tubular protein overload; receptor antagonist type one and type two all have this characteristic[94]. Bianchi and his Florence group have shown in proteinuric patients a direct relationship between aldoterone serum levels and proteinuria and a protective effect of spironolactone at a dosage of 25 mg/day in glomerular filtration rate preservation as compared to traditional therapy[95].

These data have been confirmed by Rachmani in diabetic patients treated with spironolactone 100 mg/day for 6 months and 50 mg/day for a further 6 months. Comparing the levels of proteinuria with those of a group of patients treated with ACE-I (cilazapril 5mg/day for 6 months, then reduced to 2.5 mg/day for 6 months) it has emerged that spironolactone could reduce proteinuria by 52%, against the 38% of ACE-I[96]. When aldosterone treated patients had cilazapril, another 12% reduction in proteinuria values was observed On the other hand, when spironolactone was given to cilazapril treated patients, proteinuria reduction was lower than 38%. This is essentially related to the well known "aldosterone-escape" phenomenon[96].

A protective role for aldosterone has been described also in CAN and cyclosporin toxicity. Anti-aldosterone drugs administered in phases of cyclosporin toxicity protect against both progressive reduction of renal plasma flow and GFR decline[97].

Together with the RAS system blockade, many other therapeutic approaches have been tried in order to delay dialysis need, among these, statins and fish oil[98,99]. Nevertheless so far there is no clear evidence or indications.

Research is still going forward, basic research that will give us new hints for therapeutic approaches able to reduce the velocity of sclerotic progression in kidney diseases. Among these, we list PPAR inhibitors, physiological antiflogistic molecules, rennin-specific inhibitors and vasopeptidase inhibitors (such as omopaprilat). It is important to remember, though, that all of these are physiological, complex systems that actively participate in the survival of the most complex software in the world, the human body. A complete blockade of such systems could lead to deleterious effects and it is up to us physicians to think first of our patients' lives, the most precious thing, and then of their kidney.

Primum non nocere.

CONCLUSIONS

This review did not presume to summarise all the scientific knowledge currently available, but was written with the intention of giving an overview of up-to-date acquired data and evidence-based therapeutic options, useful we hope to treat at our best our patients and postpone as far as possible the beginning of dialysis treatment.

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