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chronic kidney disease (CKD) is a significant interactive disease in patients with diabetes, hypertension, and cardiovascular disease with major morbidity and mortality consequences and high costs to the healthcare system. CKD is characterized by a gradual loss of renal function. In most parts of the world, once end-stage renal disease (ESRD) occurs, patients who do not have access to maintenance dialysis or kidney transplantation would simply die. The data reported in the registry of the Chinese Society of Nephrology indicate that 41 000 ESRD patients were receiving dialysis in 1999, accounting for only 5% of the total population requiring renal replacement therapy. Delaying the progression of CKD to ESRD is an essential management goal for the clinical practice, particularly in developing countries.

The renin-angiotensin system (RAS) blockade is currently the best-documented treatment strategy to delay the progression of CKD. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II type 1 receptor antagonists (ARBs) have been widely used in hypertensive and normotensive CKD patients with or without diabetes. However, despite great progress in this therapy, it has not been proved to stop CKD progress completely. Therefore, it is necessary to search for more optimal therapeutic strategies which can further improve renal outcome. In our experience, four principles should be kept in mind when we prescribe RAS inhibitors (RASIs) for renal protection: start early, optimal dose, long-term therapy, and combination of ACEI and ARB.

HOW EARLY SHOULD WE START TREATING CKD PATIENTS WITH RAS INHIBITORS?

Our recent study shows that in patients with basal serum creatinine of 274-442 µmol/L, 41% assigned to benazepril reached the primary composite end point of a doubling of the serum creatinine level, ESRD or death during the 3-years follow-up. However, the number of patients who reached the primary end point (21.6%) was much lower among patients with basal serum creatinine of 133-265 µmol/L, even though these patients receive the same dose of benazepril. Likewise, in a post hoc analysis of REIN study, the incidence of ESRD was higher among patients with worse baseline glomerular filtration rate (GFR) than among those with more preserved renal function. These phenomena might be explained by the fact that the RASIs-associated reduction in risk is time dependent and that patients with more advanced CKD have been treated for a shorter period than those with earlier CKD. Thus, to achieve maximal renal protection, treatment with RASIs should be initiated at earlier stages of CKD.

How early should we start to use these drugs? More attention is focused on microalbuminuria which has been demonstrated to be a predictor of both renal and cardiovascular outcome in patients with or without diabetes. In IRMA 2 study, an ARB irbesartan significantly reduce the risk of primary end point, the time to the onset of diabetic nephropathy, in hypertensive patients with type 2 diabetes and microalbuminuria. It has been widely accepted that persistent microalbuminuria, whenever occur, is an indicator for RASIs therapy.

More interesting evidence comes from recent BENEDICT. In this randomized controlled study, administration of ACEI trandolapril prevents the development of microalbuminuria in subjects with type 2 diabetes and hypertension but without microalbuminuria. These data suggest that we might have the reason to start RASIs therapy in subjects with high risk of developing CKD, such as those with diabetes, hypertension, and obesity. Dr. de Jong and Brenner suggested that the present practice of secondary prevention in those with known prior renal disease should be extended to primary prevention for those subjects in the general population who are at risk for progressive renal failure such as renal hypertrophy and high GFR.

WHAT IS THE OPTIMAL DOSE OF RASIS IN RENAL PROTECTION?

The aim of using RASIs in CKD is not only reduction of...
blood pressure, but also decrease of urinary protein excretion and retarding the progressive renal function decline.

Hypertension, especially systolic hypertension, is a strong risk factor for the progression of renal disease. The glomeruli and peritubular capillaries operate at lower pressure than systemic pressure. Consequently, adequate autoregulation of blood flow must occur to “step down” systemic pressure. This autoregulation is primarily governed by either myogenic responses of the afferent arteriole or by tubuloglomerular feedback mechanisms which are stimulated by adenosine, angiotensin II and renal sympathetic nerve activity. An understanding of renal autoregulation provides a framework for understanding the relationship between systemic blood pressure and renal injury; the option of intensive control of blood pressure, and the particular role of drugs that block the RAS.

How low should we go in controlling systolic hypertension? Although there is controversy, it is in general believed that patients with CKD might require levels of systemic blood pressure below that we have traditionally targeted in order to reduce the risk for progressive renal injury. Some investigators recommend a systolic blood pressure target should not be lower than 120 mmHg in type 2 diabetes and 110 mmHg in non-diabetes. Rigorous control of both systemic and glomerular capillary blood pressure is needed, particularly in patients with CKD and diabetes, that can predispose to impaired renal autoregulation.

In addition to effective blood pressure control, maximal reduction of proteinuria should be considered as an important target, since proteinuria (or microalbuminuria) is a prognostic and modifiable risk factor for both cardiovascular and renal disease progression. Animal studies have demonstrated that maximal renal benefit from ACEIs or ARBs requires higher doses than are needed to normalized blood pressure. Small clinical studies have shown that titrating ACEIs or ARBs to higher doses is potent in reducing proteinuria. Our recent long-term randomized controlled trial demonstrated that in nondiabetic CKD patients who have proteinuria and chronic renal insufficiency, employment of optimal antiproteinuria and tolerable doses of benazepril or losartan is associated with a significant improvement in renal outcome as compared with their conventional doses in current clinical practice. These data suggest that the recommended doses of ACEIs or ARBs in current practice, which base on their blood pressure lowering effect, might be inadequate to satisfactorily halt renal progression. This notion has been supported by the recent animal study indicating that high dose of ARB provide non-blood pressure dependent protective effect against renal fibrosis. However, the safety and tolerability profile of higher doses of RASIs need further investigation, particularly in patients with diabetes and more advanced chronic renal dysfunction.

Based on available evidence, we think that the treatment targets should differ among different comorbid groups. Actually, in most patients, achieving maximal renal protection requires a multidrug regimen, usually including several antihypertensives. Within this approach, the first step is optimal titration of RASIs aimed at optimal reduction of proteinuria.

**HOW LONG SHOULD WE TREAT THE CKD PATIENTS WITH RASIS?**

One of the most impressive findings of REIN follow up study is that after about 36 months of treatment with ramipril, no additional patients progressed to the point of requiring dialysis, whereas patients switch from conventional antihypertensive therapy to ramipril continue to develop ESRD, but the progression to ESRD can be delayed by about 5 years. These data suggest that long-term treatment with RASIs might provide more benefit for renoprotection.

Until recently, the matter of the ACEIs and ARBs administration in patients with impaired renal function has caused numerous controversies. Many physicians are reluctant to use RASIs in patients with chronic renal insufficiency because of concern that serum creatinine or potassium level will rise. This behavior is further encouraged by advice from some investigators to withhold these medications when serum creatinine level exceeds 265 µmol/L. It is estimated that below 20% of patients in need are currently offered this renoprotection therapy.

Our recent randomized controlled study in non-diabetic CKD patients demonstrates that RAS inhibition slow down the progression of renal function decline even in patients with advanced renal dysfunction. Adverse events rate in the ACEI is comparable to the placebo group. Being consistent with our results, the post hoc, secondary analysis of the REIN trial clarifies that ramipril decreases the incidence of ESRD by 33% in nondiabetic patients with basal GFR of (13.6—32.6 ml/min). Adverse events, such as worsening of renal function and hyperkalemia, are comparable among those with the lowest GFR (13.6—32.6 ml/min), medium GFR (33.0—50.8 ml/min), and the highest tertile GFR (51.7—100.9 ml/min). These data provide strong background for the recommendation to administer the RASIs to all patients with proteinuric CKD. RASIs should not be discontinued even when serum creatinine level increase exceeds 265 µmol/L during the long-term treatment. Certainly, it is strongly advised to use these drugs with increased prudence, monitoring the serum creatinine and potassium concentration.

Another question is how we should do if an early
decrease in GFR is observed after initiation of RASIs therapy. According to the K/DOQI clinical practical guidelines, a decrease in GFR by no more than 30% is acceptable. Decrement of GFR by more than 30% over baseline should result in a reduction in drug dosage and monitoring of GFR within 5–7 days. If GFR does not return to baseline values, ACEIs or ARBs should be discontinued. Restriction of intake of food rich in potassium, concomitant diuretic therapy and carefully optimizing acid-base balance can decrease the incidence of hyperkalemia. Since the type 4 renal tubular acidosis commonly associated with diabetes may predispose these patients to hyperkalemia when a RASI is added, caution is need before the application of the RASIs in patients with diabetes who have advanced CKD. The efficacy and safety has not been tested by any randomized controlled study in this patient population.

IS THE COMBINATION OF ACEI AND ARB SUPERIOR TO MONOTHERAPY IN RENOPROTECTION?

The combination of an ACEI and an ARB has been suggested as a way to maximize RAS blockade. The potential benefits of such a combination result from: (1) dual blockade of RAS at the level of angiotensin II synthesis and angiotensin type 1 receptor, respectively; (2) preventing the activation of angiotensin II type 2 receptor; (3) potentially additive benefit from increased bradykinin activity; (4) a decrease in angiotensin II amount at the tissue level; (5) preventing the “escape phenomenon” of ACEI; and (6) preventing the detrimental effects of angiotensin IV.

Recent clinical studies have demonstrated the additional antiproteinuric benefit of such combination therapy in CKD patients with or without diabetes. The COOPERATE trial has demonstrated that long-term renoprotection with dual RAS blockade is better than monotherapy, at least when fixed doses are used. Although there is a clear rationale for the use of combination therapy to achieve more complete renoprotection, the beneficial effect of the therapy has to be weighed against the risk of hyperkalemia. Further studies are necessary to evaluate the safety under combination therapy, particularly in patients with more advanced renal insufficiency. Given the financial considerations, administration of combination therapy should be reserved currently to patients with high risk of progression. In any CKD patients in whom blood pressure (<130/80 mmHg) and antiproteinuria (<1.0 g/d) targets are not achieved with monotherapy, the combination of ACEI and ARB should be recommended.

In summary, recommendation to use RASIs as the first-line therapy in patients with proteinuric CKD will stand the test of time today. Optimal use of these drugs can provide more benefit for renal protection and improve renal outcome in patients with CKD.

REFERENCES