EDITORIALES

Halting the progression of renal disease: where we stand?

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End stage renal disease (ESRD) is increasing at an alarming rate worldwide. During the last decade in the United States, the number of patients reaching ESRD jumped to 372,000[1]. Europe and Japan are expected to have a similar trend. The increase in ESRD is largely fueled by a rise in the incidence of type 2 diabetes and an aging population[2]. The epidemic of type 2 diabetes, however, is not limited to the United States, Europe and Japan. The number of adults with diabetes worldwide is expected to reach 300 million by the year 2025, with 75% of those affected in non-industrialized nations[3]. As approximately 27% of type 2 diabetics are at risk for developing nephropathy after 20 years of diabetes[4], these statistics present a staggering challenge to health care providers and patients alike. From a purely financial standpoint, ESRD care is tremendously expensive, and the cost of the U.S. dialysis program is expected to double to $28 billion US by 2010[5]. This is mirrored in Europe, where dialysis care consumes a disproportionate percentage of health care budgets[6]. The cost of providing dialysis may be prohibitive for many developing countries and for patients in these areas, ESRD means death from uremia. Even if dialysis is available, the view from the patient's perspective is grim; besides the severe life style modifications required by dialysis, those afflicted with ESRD face significant morbidity and mortality. Dialysis patients have a much short life expectancy of aged matched controls, with cardiovascular disease being the largest single cause of death[5]. Patients starting dialysis are also older and sicker; the average age of a patient on dialysis in the United States had risen to 62 years from 58 years during the last decade, and more than 30% have a history of ischemic heart disease[7]. The increase in morbidity and mortality from renal disease is not limited to those with ESRD; chronic renal insufficiency (CRI) itself is also a risk factor for cardiovascular disease, and patients with microalbuminuria, increased serum creatinine or decreased creatinine clearance are at greater risk for cardiovascular disease than those without[8]. Clearly, the best solution to the problems of CRI and ESRD is to find effective therapies to slow the progression of established nephropathy, and in diseases where nephropathy is likely to develop, to find strategies to prevent its emergence.

There are effective treatment options available today for patients with both diabetic and non diabetic chronic nephropathy. Hypertension and proteinuria have emerged as major factors that predict the risk of progression to ESRD and treatment of these disorders is renoprotective. Hypertension, also an independent cardiovascular risk factor, was found in the MDRD study to predict the risk of progression of CRI in non-diabetic chronic renal insufficiency[9]. Both type 1 and type 2 diabetics with elevated blood pressure are at higher risk for progression, and treatment of elevated blood pressure reduces this risk[10]. Proteinuria, once thought to be merely a marker of renal disease, has been also established as a major risk factor in identifying patients at risk for progressing to ESRD[9]. Excessive filtered proteins causes inflammation and scarring in the proximal tubules and interstitium, which ultimately may lead to ESRD[11] and agents that decrease proteinuria are renal protective[12]. Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin 2 receptor antagonists (ARA) have been shown in a number of studies for both diabetic and non diabetic patients to reduce proteinuria in a mechanism that is not directly linked to reduction of systemic blood pressure[11]. The REIN trial, which investigated the effect of ACE-I *vs* conventional blood

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pressure control, found that treatment with ACE-I reduced proteinuria, and resulted in a sustained slowing of the loss of GFR[13]. This study also included patients with severely impaired renal insufficiency, and found that these patients benefited from ACE-I with an acceptable side-effect profile[14]. ACE-I have similar benefits in type I diabetic nephropathy and slow progression to ESRD[15]. The recently published RENAAL[16] and IDNT[17] trials also demonstrated a beneficial effect of treatment with ARA in the treatment of overt type 2 diabetic nephropathy. These trials included patients with a maximum serum creatinine of 3.0 mg/dL and had a relatively low rate of side effects such as hyperkalemia. ARA also successfully slowed the development of diabetic nephropathy in type 2[18] and ACE-I in type 1[19] diabetic patients with microalbuminuria. These drugs are also cost effective, and are associated with significant cost savings[20,21].

In addition to reducing proteinuria, agents that block the RAS also have significant cardioprotective benefits. ACE-I and ARA are effective in treating congestive heart failure, and in the HOPE trial, treatment with ACE-I was shown to effectively reduce the risk of death from cardiovascular causes in patients at risk for cardiac disease[22]. The non-diabetic patient group that received the ACE-I in the HOPE trial also developed less diabetes than the control group, for reasons that are not fully understood[23].

Unfortunately, not all patients respond to these measures. In the IDNT[17] and RENAAL[16] trial, 14.2% and 19.6% respectively, of patients in the ARA group still progressed to ESRD. The REIN trial found that women responded better to ACE-I than men, and that ACE genotype was important in predicting a male patient's response[24]. Preliminary data suggest that an aggressive, multi-system approach of blood pressure control, blockade of the RAS, treatment of dyslipidemia and smoking cessation[11,25] may be renal protective in these patients. Newer therapies are being developed to address the needs of those who do not respond to ACE-I or ARA and include endothelin antagonists and vasopeptidase inhibitors[11].

Despite these advances, many patients are not aggressively treated for hypertension, proteinuria and renal insufficiency. In the general U.S. population, control of elevated blood pressure is very poor and less than 25% of hypertensive patients have their blood pressure at target levels of < 140/90[26]. These data include all patients; little is known about the adequacy of control in those with renal insufficiency. A recent study of 1,247 type 2 diabetics with hypertension had similar findings; only 26.7% met the target goal of 130/85[27]. Some physicians seem unaware of the risk/benefit ratio of treatment with ACE-I or ARA. There are misconceptions regarding the safety of ACE-I use in patients with renal insufficiency, with some authors suggesting that they not be used in patients with creatinine levels greater than 3 mg/dL[28]. Acute renal failure due to bilateral renal artery stenosis and hyperkalemia are often feared[29], despite the safety profiles of the clinical trials using ACE-I and ARA in patients with renal disease[13,16,17]. One recent study found that in patients with congestive heart failure, ACE-I were less likely to be prescribed when the serum creatinine was greater than 3 mg/dL[31]. Interestingly, this study found that the patients who benefited the most from ACE-I use were those with a serum creatinine > 3 mg/dL. While it would be easy to blame this approach on non-nephrologists, evidence suggests that[32] nephrologists are just as likely not to prescribe an ACE-I for patients with renal insufficiency as primary care physicians. Improved physician education is strongly needed to ensure that patients with renal insufficiency benefit from the available proven treatment strategies to reduce the risk of ESRD. A concerted, sustained effort to prevent progression to ESRD is needed if we are to reduce the burden of dialysis. Physicians must be aware that there are powerful tools to reduce, and perhaps halt, progression to ESRD and we should not hesitate to use them.

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