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ESCAPE: From Hypertension to Renal Failure

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Abstract

ESCAPE Trial Group, Wühl E, Trivelli A, et al.: Strict blood-pressure control and progression of renal failure in children. *N Engl J Med* 2009, 361:1639–1650.

Introduction

Hypertension is a major risk factor for the development and progression of chronic kidney disease leading to renal loss and a requirement for dialysis or kidney transplantation [1]. This concept applies to both adults and children [2]. Previous studies have demonstrated involvement of the renin-angiotensin system (RAS) in the development of kidney disease [3]. Blockade of the RAS was shown to slow down the progression of diabetic and nondiabetic renal disease [4, 5]. However, most of the studies evaluating the influence of blood pressure reduction or RAS blockade have been done in adults. Currently knowledge about the effect of blood pressure reduction on the progression of renal disease in children is very limited because chronic kidney disease and hypertension are uncommon in children. It is estimated that hypertension is present in about 50% of children with chronic kidney disease [6], and both hypertension and proteinuria are associated with loss of renal function in children.

Aims

The Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of Chronic Renal Failure in Pediatric Patients (ESCAPE) trial evaluated the efficacy of intensive blood pressure control with a high-dose angiotensin-converting enzyme (ACE) inhibitor in reducing the progression of kidney disease in children with renal diseases of varying etiologies.

Methods

This randomized, controlled trial evaluated whether the effects of intensified blood pressure control, as demonstrated by achieving 24-hour blood pressure levels in the low normal

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range, would reduce progression of renal disease in children with chronic kidney disease who received fixed-dose ACE-inhibition treatment.

Initially, the ESCAPE trial was designed as a 3-year study with a single interim analysis after 2 years. However, when the interim analysis showed better-than-expected slowing of the overall rate of progression of renal disease, the study was extended to 5 years.

The active phase of the study included 385 patients, who were randomized to either intensified blood pressure control or conventional blood pressure control. All patients met the recruitment criteria of being 3–18 years of age, with stage II to stage IV chronic kidney disease (glomerular filtration rate [GFR], 15–80 mL/min/1.73 m² of body-surface area) and elevated 24-hour mean arterial pressure or hypertension controlled by antihypertensive medication. All patients received the highest dose of the ACE inhibitor ramipril. Patients with loss of GFR greater than 3 mL/min/1.73 m² per year were considered to be losing renal function quickly, whereas those losing less than 3 mL/min/1.73 m² per year were considered to have slow loss of renal function. The intensified blood pressure control was defined by a blood pressure target less than the 50th percentile, and conventional blood pressure control was defined as a blood pressure target between the 50th and 90th percentile of 24-hour mean arterial pressure. Conventional blood pressure measurement, GFR, and urinary protein excretion were monitored every 2 months. Ambulatory blood pressure monitoring was performed every 6 months. Adding other antihypertensive drugs, except for RAS blockers, was allowed. The study's primary end point was time from attainment of the full dose of ramipril to 50% reduction in GFR or progression to end-stage renal disease (GFR <10 mL/min/1.73 m² or start of renal therapy). Secondary end points included changes in blood pressure, GFR, and urinary protein excretion.

Results

Compared with baseline, the mean arterial blood pressure at 6 months was significantly lower in response to treatment and there were no differences between the responses of the two groups. This finding was confirmed by ambulatory blood pressure monitoring. However, there was a difference in mean blood pressure between the two groups after 12 months and throughout the rest of the study (range 2.7– 3.9 mm Hg). The group with intensified blood pressure control demonstrated a 70.1% delay in the progression of renal disease, compared with 58.3% for the conventional group. The GFR rate was reduced by 1.1 ± 7.8 mL/min/1.73 m² in the group with intensified blood pressure control, versus a reduction of 2.5 ± 5.9 mL/min/1.73 m² in the conventional-control group. Despite an initial reduction in urinary protein excretion in the first 6 months of the study and persistent excellent blood pressure control, proteinuria gradually increased again over the following 36 months; by the end of the study, these levels did not differ from the starting baseline levels.

Discussion

Intensified blood pressure control in children with chronic kidney disease and receiving a maximum dose of ACE inhibition delays progression of kidney disease. Despite excellent blood pressure control, proteinuria reappeared after 6 months of treatment.

Comments

The ESCAPE trial clearly demonstrates the importance of excellent blood pressure control in reducing the progression of renal disease. This concept has been repeatedly shown in adults with renal disease and is now confirmed in children. This trial also illustrates the dissociation between excellent blood pressure control and the reappearance of proteinuria in children with chronic kidney disease, despite treatment with a maximum dose of an ACE inhibitor. This is an interesting and unexpected finding, which suggests a mechanism contributing to the development of proteinuria that is independent of blood pressure. These mechanisms could vary based on the underlying kidney disease. In patients with diabetic nephropathy, the reduction in albuminuria continued during inhibition of the RAS with an angiotensin receptor blocker for up to 2 years [4]. Clearly, the ESCAPE trial investigated a nondiabetic population, and its results cannot be extended to adults, particularly those with diabetic nephropathy. However, similar to adult studies, this trial confirms the renoprotective effects of RAS blockade.

The ESCAPE trial raises several issues. First, changes in GFR were estimated in a portion of the children studied. Ideally, because the GFR is used to determine the primary and secondary end points, it should be evaluated through direct measurement to ensure maximum accuracy. Second, although the study lasted for 5 years, longer and larger studies may be needed to evaluate whether the recurrence of albuminuria stays the same or changes (up or down) and to assess the effect of these changes on renal outcome. Third, future studies with angiotensin receptor blockers or direct renin inhibitors should be planned, because they have different mechanisms of action. Fourth, it is uncommon to demonstrate a reduction in the progression of renal disease while there is a reappearance or progression of proteinuria. One would expect the proteinuria “escape” to coincide with the progression of the renal disease. Thus, further studies are needed to explain this phenomenon.

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