“Missing heritability” has become the holy grail in the search for genetic variants underlying type 2 diabetes. Genome-wide association studies have linked over 60 commonly occurring susceptibility loci to type 2 diabetes, but the impact of each of these variations is modest. These commonly occurring variants represent only about 10 percent of overall risk for developing the disease, said Mark McCarthy, MD, professor of diabetic medicine at the University of Oxford. McCarthy is one of the leaders of an international research consortium with a unique approach to identifying missing heritability, that is, the genetic variants that rarely occur in the population but that may have much stronger effects on type 2 diabetes disease risk than do the common variants thus far identified.

The consortium’s approach is to sequence and analyze the whole exomes—or coding portions of genes—of 10,000 individuals of five major ancestry groups: African American, East Asian, European, Hispanic, and South Asian. The search for the variants that influence an individual’s genetic predisposition for developing type 2 diabetes and renal disease requires such large population studies and often many years of work, said Arlene Chapman, Continued on page 4

Losartan Fails to Prevent Allograft Fibrosis and Loss in Transplant Recipients

By Tracy Hampton

Angiotensin II blockade can slow the progression of chronic kidney disease, but how effective is it in kidney transplant recipients? Investigators recently completed a large, randomized placebo-controlled clinical trial that looked at this very question.

“Contrary to what has been observed in native kidney disease, angiotensin II blockade did not demonstrate a statistically significant benefit in lessening fibrosis or terminal kidney failure from severe fibrosis,” said first author Hassan Ibrahim, MD, professor in the division of renal diseases and hypertension at the University of Minnesota, Twin Cities campus. “Nevertheless, angiotensin II blockade was safe and well tolerated.”

The study, which is published in the Journal of the American Society of Nephrology, provides valuable information that can be used to design future interventional trials to treat kidney transplant recipients.

Trial design and results

Immunosuppressants help prolong the function of transplanted organs, but thera- Continued on page 2
Losartan
Continued from page 1
pies that target non-immunological damage to these organs—such as elevated blood pressure and tissue fibrosis—have not been studied. Because angiotensin II blockade, which causes blood vessels to dilate, can slow the progression of kidney disease in the nontransplant setting, Ibrahim and his colleagues reasoned that the strategy should also be tested in transplant recipients.

“With our knowledge this is the first randomized placebo-controlled trial of angiotensin II blockade in these patients,” Ibrahim said.

The rationale for the trial rested on the hypothesis that blocking the fibrogenic effects of angiotensin II and ameliorating the hemodynamic consequences of reduced nephron number would reduce structural damage in transplanted kidneys.

The trial included 153 kidney transplant recipients who received either 100 mg of losartan per day or placebo within 3 months of transplantation. Treatment continued for 5 years. Losartan blocks the receptor for angiotensin II, an important factor involved in the renin-angiotensin-aldosterone system, which is a complex hormone system that regulates blood pressure and fluid balance.

A key premise of the trial was that losartan would exert a beneficial effect independently of its blood pressure–lowering properties, so every effort was made to keep blood pressure levels similar in the two treatment groups. This involved treating patients with calcium-channel blockers, followed by diuretics as second-line therapy and β-blockers as third-line therapy.

The primary outcome of the trial was a composite of doubling of the cortical interstitial compartment (a precursor of fibrosis) from baseline to 5 years or end stage renal disease from interstitial fibrosis and tubular atrophy, previously termed chronic allograft nephropathy. In the intention-to-treat analysis of patients with adequate structural data, the primary end point occurred in six of 47 patients who received losartan and 12 of 44 patients who received placebo, but the investigators found no significant effect of losartan on time to a composite of end stage renal disease, death, or doubling of creatinine level. In a secondary analysis, losartan seemed to reduce the risk of a composite of doubling of interstitial volume or all-cause end stage renal disease by 64 percent, but this finding requires validation.

Additional studies warranted
Although losartan was not associated with a statistically significant benefit in the primary outcome, it was well tolerated. Despite a higher level of serum potassium, only one case of severe hyperkalemia (potassium level greater than 6 mEq/L) occurred. Serum potassium levels were consistently 0.1 to 0.3 mEq/L higher in the losartan group, and hyperkalemia was observed intermittently in 17 of 77 (22.1 percent) patients in the losartan group and 5 of 76 (6.6 percent) patients in the placebo group. A total of 291 adverse events were reported, averaging 1.71 per participant in the losartan group and 2.09 in the placebo group.

According to the authors, a possible explanation for the lack of a clear and robust benefit of losartan, which has been observed in relatively advanced native kidney disease, is that this study was a primary prevention trial that included many relatively low-risk patients, mostly white recipients of live-donor kidney transplants who had low immunologic risk.

They also noted that the degree of interstitial expansion in the patients in this study was less than what has been described in the literature. The study’s original sample size estimate and power calculations predicted that 60 percent of placebo-treated patients would double their cortical interstitial fractional volume or develop end stage renal disease from interstitial fibrosis and tubular atrophy, but at the end of the trial, fewer patients than expected reached that end point.

“The event rate in the trial was much lower than what was expected, which affected the statistical power of our findings,” Ibrahim said.

The investigators concluded that the trend toward a treatment benefit from losartan and the lack of clear harm supports the performance of a larger clinical trial. In this regard, the findings

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provide valuable information for future studies of non-immunological therapies for kidney transplant recipients.

Consensus among experts

“Although the study had a negative result on the primary prevention of interstitial fibrosis and tubular atrophy, it showed the excellent tolerance of losartan in these patients with a good control of blood pressure,” said Joseph Campistol, MD, director of the Clinical Institute of Nephrology and Urology at the Hospital Clinic in Barcelona. “With these results in mind, the antihypertensive treatment in transplant patients could be re-evaluated.”

Ibrahim noted that results from a similar ongoing trial in Canada should provide additional information on the potential role of angiotensin II blockade in these patients.

Study co-authors include Scott Jackson, MS, Jeffrey Connaire, MD, Arthur Matas, MD, Arthur Ney, MD, Ann West, RN, Nicole Lentsch, RN, Jensina Erickson, Jenny Bodner, RN, Bertram Kasiske, MD, FACP (Hennepin County Medical Center); Behzad Najafian, MD (University of Washington); and Michael Mauer, MD (University of Minnesota).

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