

Gene Polymorphism Influences Response to Angiotensin Blockade

Based on a presentation by Gershan K. Davis, MD

Presentation Summary

Researchers have been examining the role of the angiotensin converting enzyme (ACE) gene insertion/deletion polymorphism and the role of the gene DD genotype in different cardiovascular diseases. Specifically, a limited number of small studies have examined the effects of these genetic variants in response to treatment with drugs that affect the

renin angiotensin system.¹⁻³

Since recent research has concluded that the angiotensin converting enzyme DD genotype may be associated with a poor response to ACE inhibitor treatment, a pilot study was undertaken to determine the effect of the angiotensin II receptor blocker losartan on the hypotensive response in patients with different ACE genetic variants.⁴

Attention is focused on the response of angiotensin converting enzyme (ACE) genetic variants to treatment with drugs affecting the renin angiotensin system, including ACE inhibitors. "Although the research is quite limited at the moment, the results so far suggest a poor response among those with the DD genotype to ACE inhibitor treatment for diabetic renal protective therapy and for heart failure," explained Gershan K. Davis, MD.⁵ "Furthermore, the response in hypertension to ACE inhibitor treatment among those with ACE genetic variants has been mixed so far."

Indeed, some studies show that the DD variant actually affords a better response to ACE inhibitor treatment in terms of blood pressure lowering, reduction in left ventricular mass, and indices of diastolic dysfunction, while other reports show no effect, Dr. Gershan explained.⁶

Pilot Study

Working under the assumption that the DD genotype of ACE polymorphism adversely affects response to ACE inhibitors, Dr. Davis and fellow researchers at the Cardiac Centre, Blackpool, England, and University of Manchester, England, examined pilot study data to determine whether the DD ACE variant also influences response to treatment with an angiotensin II receptor blocker. The parameters of blood pressure lowering and left ventricular mass were evaluated, and the drug used was losartan.

Subjects for the study included 28 patients with persistent hypertension who had been referred by general practitioners to a regional cardiac center for investigation and treatment, Dr. Davis said. Of the 28 patients, 19 were men. Patient age ranged from 29 to 72 years with a mean of 57 years.

The mean duration of hypertension among the study patients was 6.5 years, and 60% had a family history of the disorder. A high percentage of the patients had previous changes in blood pressure medication because of side effects, and 36% of the group had received no previous blood pressure therapy.

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— Gershon K. Davis, MD

All patients had clinical blood pressure readings of 140/90 mmHg or higher at study entry. When 24-hour blood pressure measurements were taken prior to initiation of study medication, the overall pressure was 149/89 mmHg.

Left ventricular mass and left ventricular mass index were determined by echocardiography prior to treatment, and ACE genotype was determined by polymerase chain reaction. The patients were then divided according to genotype II, ID, or DD. "There were no significant differences in age, systolic blood pressure, or diastolic pressure between the three genotype groups," Dr. Davis said.

Patients who had no history of previous blood pressure medication use received 50 mg losartan daily in this study. Those who were already taking blood pressure medication received 50 mg losartan daily in addition to their usual treatment. The treatment period was 6 months.

Results

Data were presented on 18 patients: six were of ACE genotype II, seven had genotype ID, and five were of genotype DD. "After the 6 months of treatment with losartan, the mean 24-hour systolic blood pressure was reduced in the overall group by 10.4 mmHg ($P < 0.005$), and diastolic blood pressure was reduced by 5.2 mmHg ($P < 0.01$)," Dr. Davis reported.

"The difference in systolic blood pressure reduction between the three genotype groups was not statistically significant. Differences between groups in terms of reduction in diastolic blood pressure were not significant, but when we looked at patients in terms of which ones achieved greater diastolic blood pressure reduction, it was significant for the II genotype group," he explained. More genotype II patients had a reduction in diastolic pressure greater than 10 mmHg, with a trend toward greater reduction with the I allele, according to Dr. Davis.

At baseline, mean left ventricular mass index had been 125 for those with ACE genotype II, 126 for genotype ID patients, and 137 for patients with ACE genotype DD. After 6 months of treatment with losartan, 50% of patients achieved a reduction in mean left ventricular mass index with the greatest reduction being 40 g/m. Of the patients showing a reduction, 66% were ACE genotype II, 57% were genotype ID, and only 20% were of genotype DD.

"The results of our small study suggest that ACE gene polymorphism influences the hypotensive response to an angiotensin II receptor blocker, and it appears that the II genotype patient may achieve better results with larger reductions in diastolic blood pressure and left ventricular mass," Dr. Davis said. However, Dr. Davis said that there is an AII receptor polymorphism that may also influence response to these drugs. Dr. Davis concluded that "Large-scale studies in different cardiovascular conditions are required to confirm whether polymorphisms of renin angiotensin system

genes can predict patient clinical response to drugs (ACE inhibitors and angiotensin II antagonists), which act on this most important homeostatic system.”

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