Valsartan Lowers Serum C-Reactive Protein Levels

Results suggest that an anti-inflammatory effect by the angiotensin II receptor blocker may be responsible.

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW YORK — Monotherapy with valsartan has been shown for the first time to lower serum levels of C-reactive protein, raising the possibility that valsartan—and possibly other antihypertensive agents—might have a beneficial effect on cardiovascular events that goes beyond blood pressure reduction.

Results from Val-MARC (Valsartan-Managing Blood Pressure Aggressively and Evaluating Reductions in hsCRP) also showed that valsartan's effect on C-reactive protein (CRP) was independent of blood pressure reduction, suggesting that a pleiotropic, anti-inflammatory effect by this angiotensin II receptor blocker (ARB) might have produced the result. And in the study, with more than 1,600 patients, concurrent treatment with the popular diuretic hydrochlorothiazide (HCTZ) plus valsartan appeared to blunt the CRP reduction, raising questions about possible adverse, pleiotropic effects of HCTZ.

"The current data raise the hypothesis that some antihypertensive regimens may have additional anti-inflammatory properties," Dr. Paul M. Ridker reported at the annual meeting of the American Society of Hypertension. "Whether this translates to a net clinical advantage will require well-designed, prospective trials of hypertension treatment that specifically target" patients with elevated CRP levels, said Dr. Ridker, director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital in Boston.

Results from the landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) "suggested that HCTZ is an excellent antihypertensive drug in a study that enrolled all comers," said Dr. Ridker, who is also the Eugene Braunwald Professor of Medicine at Harvard Medical School in Boston. We now need to do large trials to see if the potential exists for real differences in the effects of HCTZ, ARBs, and ACE inhibitors in patients with an enhanced, innate immune response that might have been masked in ALLHAT by enrolling all comers, he said.

The study enrolled patients with stage 2 hypertension at 384 U.S. centers from January 2004 to June 2005. Patients were randomized in an open-label fashion, with 836 assigned to 320 mg valsartan daily, and 832 assigned to receive daily treatment with 320 mg valsartan and 12.5 mg HCTZ. The study's primary end point was blood pressure reduction and changes in serum levels of CRP after 6 weeks. It was sponsored by Novartis Pharmaceuticals, which markets valsartan (Diovan). Dr. Ridker has received research support from Novartis and is co-owner of a patent for a CRP test.

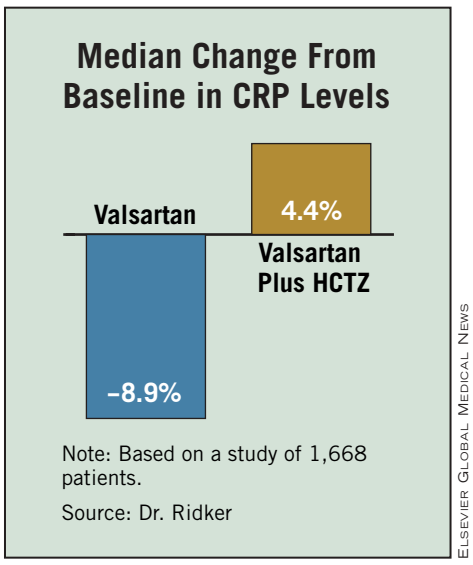
After 6 weeks, valsartan monotherapy cut systolic pressure by an average of 18 mm Hg, compared with an average drop of 25 mm Hg in patients on the combined regimen. The percentage of patients who reached the goal pressure target of 140/90 mm Hg or less was 32% in the monotherapy group and 48% in the valsartan plus HCTZ group. Simultaneously with Dr. Ridker's report at the meeting, these results were published online (Hypertension 2006 [doi:10.1161/01.HYP.0000226046.58883.32]).

CRP measurements showed that patients treated with only valsartan had a median reduction in their serum level of 0.12 mg/L, a reduction of 8.9% from baseline. In contrast, among patients treated with valsartan plus HCTZ, the median change in CRP was an increase of 0.05 mg/L, a median rise of 4.4%. The difference in the change in CRP levels between the two groups was statistically significant.

"We saw no relationship whatsoever between the extent of blood pressure reduction and the extent of CRP reduction," Dr. Ridker said. "The data lead to the hypothesis that valsartan reduces inflammation in a way that's independent of blood pressure reduction." In addition, the almost 9% median drop in CRP seen in the valsartan-only group was comparable to the reduction in CRP that's been linked to statin treatment.

The effect of valsartan alone and of valsartan plus HCTZ on CRP levels was "remarkably consistent" across every patient subgroup examined, including patients who were also treated with statins and those who were not, he said. This last observation suggests that the ability of valsartan alone to lower CRP levels is independent of the action of statins, and so the two effects might be additive.

Although Dr. Ridker acknowledged that CRP-lowering may be a class effect for all ARBs, he stressed that so far the effect has been proved only for valsartan: "We've been [wrong] about class effects for statins; it may not be as simple as we once thought." ARBs were hypothesized to have an effect on CRP because of angiotensin II's proinflammatory effects. (ARBs block the angiotensin II receptor.)



ELSEVIER GLOBAL MEDICAL NEWS

It's unclear whether other antihypertensive drugs—including the ACE inhibitors, calcium channel blockers, and β-blockers—also exert anti-inflammatory effects, Dr. Ridker said. It's also unclear what effect HCTZ might have on inflammatory processes. The drug is known to boost insulin resistance, the incidence of diabetes, and serum levels of plasminogen activator inhibitor-1. All of these activities track with elevated CRP levels, but it's too soon to say whether this explains the study's results, Dr. Ridker said. Even if HCTZ is eventually shown to block a beneficial reduction in CRP levels, and despite the drug's other adverse effects, physicians will probably find it hard to avoid using the drug in patients with refractory hypertension.

"In many patients with hypertension, it's extremely hard to get them to their goal pressure without a diuretic," commented Dr. Joel M. Neutel, medical director of clinical pharmacology at the Orange County Research Center in Tustin, Calif. ■

Combination Therapy Works Better for Hypertension Control

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW YORK — Combination antihypertensive therapy must be used more aggressively as the first-line treatment for patients, especially those with diabetes, Dr. Joel M. Neutel said at the annual meeting of the American Society of Hypertension.

"We know that we need combination therapy to get patients to their goal blood pressure, but in practice [physicians in the United States] are very reluctant to titrate multiple drugs," said Dr. Neutel, medical director of clinical pharmacology at the Orange County Research Center in Tustin, Calif. "We need to be much more aggressive with combination therapy," he said. "All the evidence shows that there is no increase in adverse effects with more aggressive treatment."

The added value of a two-drug combination compared with monotherapy was documented by two separate studies reported by Dr. Neutel at the meeting. One study examined adding amlodipine to treatment with either quinapril or losartan. The second study looked at the effect of adding the angiotensin II receptor blocker (ARB) irbesartan to the diuretic hydrochlorothiazide (HCTZ).

Dr. Neutel acknowledged that the results from many prior studies had already proved the added efficacy and safety of combination therapy, but he stressed the importance of adding to this evidence base.

"We need to provide physicians with a lot of data to make them comfortable with the fact that we can have better blood pressure control with complementary combinations of drugs." Only about half of U.S. patients with diagnosed hypertension are on medical treatment, and of those only about one-third have their blood pressure controlled to their goal level, he noted. Among patients with diabetes, fewer than 20% are at their goal pressure, which was set at less than 130/80 mm Hg in the National Heart, Lung, and Blood Institute's Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).

"With more reports, we hope that physicians will be more willing to use combination therapy and use it as first-line therapy," he said.

The first study enrolled diabetic patients with a systolic pressure of 140-170 mm Hg and a diastolic pressure of 90-110 mm Hg who were not on any treatment. Patients with a pressure of more than 135/80 mm Hg who were uncontrolled on either monotherapy or combination therapy were also included.

Patients were initially treated with either 20 mg/day of the ACE inhibitor quinapril or 50 mg/day of the ARB losartan. After 4 weeks, the daily dosages were titrated to 40 mg quinapril or 100 mg losartan. After another 4 weeks, patients were randomized to either 5 mg/day of amlodipine or placebo. After 6 weeks, the amlodipine dosage was increased to 10 mg/day.

The primary end point was the percentage of patients whose blood pressure was below 130/80 mm Hg after 6 weeks of treatment on the final, titrated regimen. This goal was met by 27.5% of the 211 patients in the combination-therapy group, and by 12.5% of the 200 patients treated with just one drug, a statistically significant difference. The combination regimens were as safe as monotherapy, with no excess incidence of adverse effects, Dr. Neutel reported.

The second study randomized nondiabetic patients to either combination therapy with 150 mg/day irbesartan plus 12.5 mg/day HCTZ, or to monotherapy with the ARB irbesartan alone at a dosage of 150 mg/day. After 1 week, the dosage received by all patients was doubled, to 300 mg of irbesartan plus 25 mg HCTZ or to 300 mg of irbesartan alone. The primary end point was the percentage of patients with a diastolic pressure of less than 90 mm Hg after 5 weeks of treatment.

This goal was reached by 47% of the 423 patients in the combination arm, and by 33% of the 206 patients in the monotherapy group, a statistically significant difference. The study's secondary end point was the percentage of patients with a pressure of less than 140/90 mm Hg, which was reached by 35% of patients on combination therapy and by 19% of those on monotherapy.

The adverse-effect profile and severity was similar in the two treatment groups, Dr. Neutel said.

The next step in the development of combination therapies is to run studies that directly compare the safety and efficacy of different drug combinations, he said. ■