Drug Monitor

Dual vs. Single Blockade in Diabetic Hypertension

Theoretically, the advantage of supplementing angiotensin converting enzyme (ACE) inhibitor therapy with an angiotensin II receptor blocker in diabetic patients with hypertension is that it reduces the occurrence of "ACE" escape (a phenomenon in which angiotensin II and aldosterone levels rise despite continuing ACE inhibitor therapy) while preserving the ACE inhibitor's effect on bradykinin degradation. The Candesartan and Lisinopril Microalbuminuria (CALM) study was one of the first to demonstrate clinical benefits with this type of dual blockade. But until now, it was unclear whether these benefits would persist over a longer period of treatment.

The CALM II study, a prospective, randomized, parallel-group, double-blind trial, compared the combination of candesartan 16 mg/day plus lisinopril 20 mg/day with lisinopril 40 mg/day in 75 hypertensive patients with diabetes (type 1 or 2) for one year. Patients were allowed to continue taking other antihypertensives during the study, but the only adjustment permitted for persistently high blood pressure was the addition of bendroflumethiazid 2.5 mg.

The researchers found no significant differences between the two treatments in terms of either efficacy or safety. Both reduced systolic blood pressure and stabilized patients' urinary albumin-to-creatinine ratio, and both were well tolerated with similarly low rates of adverse effects. While dual blockade treatment tended to be more effective on daytime, 24-hour, and night systolic blood pressure, the trend was not significant.

Source: *Diabetes Care*. 2005; 28:273–277.

Imatinib for Kaposi Sarcoma: A Mixed Blessing

The results are promising, but the regimen definitely needs some fine tuning. That's the upshot of a recent trial of imatinib mesylate in 10 men with AIDS-related Kaposi sarcoma (KS) conducted by researchers from Beth Israel Deaconess Medical Center and Perkin Elmer Life Sciences, Boston, MA; Cell Signaling Technology, Beverly, MA; and the University of Pittsburgh Cancer Institute, Pittsburgh, PA. While the drug stopped or slowed development of cutaneous lesions within a month, the trade-off for most of the patients was severe diarrhea.

After four weeks of treatment, five patients experienced a partial tumor response, and the other five (who had been developing new lesions before starting imatinib therapy) had their disease stabilized. Of the three patients in the latter group who had biopsies after four weeks, two had results that showed histologic regression.

All 10 patients, however, required a reduction in the initial imatinib dosage (from 300 mg twice daily to 200 mg twice daily), primarily because of diarrhea. Five patients experienced grade 3 or 4 diarrhea, typically in the second or third week. One patient developed grade 4 neutropenia and one developed grade 3 depression. In all of these cases, the adverse effects recurred despite drug withdrawal and dosage reduction—though the severity of diarrhea was reduced through the use of antimotility agents.

The researchers found no infectious causes of diarrhea. They suggest that the increased frequency and severity of diarrhea in this study, compared with previous studies in patients with chronic myelogenous leukemia, might have been caused by an interaction between imatinib and the patients' highly active antiretroviral therapy. Imatinib is a substrate for the cytochrome p450 isoforms CYP3A4 and CYP2D6. All of the protease inhibitors approved at the time of the study (including amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir) are CYP3A4 inhibitors, and ritonavir is a lesser inhibitor of CYP2D6. Diarrhea is a common adverse effect for all of the protease inhibitors. The researchers found no correlation, however, between any specific antiretroviral regimen and the incidence of diarrhea in this study. ●

Source: *J Clin Oncol*. 2005; 23:982–989.