Pipeline for Heart Failure Drugs Is Chock Full

BY BRUCE JANCIN
Denver Bureau

VANCOUVER, B.C. — The recent big therapeutic successes in heart failure have come from implantable electrophysiologic devices—cardiac resynchronization therapy, implantable cardioverter defibrillators—and surgical advances, such as ventricular reduction procedures.

Although attempts to develop new drugs have been disappointing lately, that may be about to change, Robert E. Hobbs, M.D., said at a meeting sponsored by the International Academy of Cardiology.

Many heart failure drugs are wending through the developmental process. Each listed here has shown promise in clinical trials, and each addresses a different hypothesis about the nature of worsening heart failure; however, they constitute only a portion of what's in the pipeline, said Dr. Hobbs of the Cleveland Clinic Foundation.

► **A xanthine oxidase inhibitor.** Oxypurinol, an analogue of allopurinol, inhibits xanthine oxidase, the enzyme that produces uric acid, as well as harmful oxygen free radicals. Xanthine oxidase is upregulated in heart failure. By inhibiting this enzyme, oxypurinol has been shown to improve myocardial energetics and endothelial function.

The Oxypurinol Therapy for Congestive Heart Failure (OPT-CHF) trial is a recently completed 400-patient phase II/III randomized double-blind trial. The data are now being analyzed and are due to be presented this fall at the annual meeting of the American Heart Association.

► **A unique inotropic agent.** Levosimendan's mechanism of action differs from that of other inotropes, such as dobutamine and milrinone. It binds to cardiac troponin C. Levosimendan is categorized as a calcium-sensitizing agent because it enhances myocardial contractility without increasing intracellular calcium concentrations. The drug also acts as a vasodilator through activation of potassium channels. Moreover, it's a weak phosphodiesterase inhibitor as well.

Levosimendan's hemodynamic effects include an increase in cardiac index along with systemic and coronary vasodilation. In heart failure patients, levosimendan reduces elevated intracardiac pressures without increasing myocardial oxygen consumption. Unlike other inotropes, it has low arrhythmic potential, he stressed.

Levosimendan is approved for use in more than 30 countries as a treatment for patients with decompensated heart failure in need of inotropic support. But not in the United States.

An intravenous version of levosimendan is being studied today. The 800-patient phase-III Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE) trial is due to be presented in November at the AHA meeting.

► **A thyroid hormone analogue.** Roughly 30% of patients with advanced heart failure have low T_3 and normal TSH. Giving T_3 to patients with heart failure confers multiple cardiovascular benefits, including positive inotropic effects, improved diastolic relaxation, and stimulation of alpha-myosin heavy chain gene expression. But it also causes tachycardia, largely negating the improved cardiac performance.

Treatment with 3,5-diiodothyropropionic acid (DITPA), a T_3 analogue, offers similar cardiovascular benefits—but without the tachycardia. A 40-center, 34-week randomized trial is underway in 150 patients with class III/IV heart failure, low ejection fraction, low T_3, and normal TSH. Participants are assigned to one of two doses of DITPA or placebo.

► **Adenosine receptor antagonists.** These agents cause afferent arteriolar dilatation. They promote diuresis while preserving renal function and maintaining glomerular filtration rate. One agent—known only as KW-3902—is the subject of an ongoing clinical trial in 200 hospitalized heart failure patients with impaired renal function. It's a 4-day treatment study with 30-day follow-up.

► **Vasopressin antagonists.** Nicknamed "super diuretics," these drugs cause profound diuresis without disrupting electrolytes. The target of these drugs (vasopressin) is synthesized by the hypothalamus in response to baroreceptor and osmotic stimuli. It causes vasoconstriction and sodium and water retention.

Two vasopressin antagonists, or "vaptans," have been tested in clinical trials: conivaptan and tolvaptan. Results are probably several years off, according to Dr. Hobbs. ■

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