New Evidence Supports Ranolazine for Angina

The drug showed no increase over placebo in all-cause or sudden cardiac death, and it reduced arrhythmias.

BY BRUCE JANCIN
Denver Bureau

NEW ORLEANS — Ranolazine may have earned a product labeling upgrade from second-line to first-tier status for treatment of chronic angina on the strength of its safety performance in the 6,560-patient MERLIN trial.

"Safety concerns have been at the forefront for this agent," Dr. David A. Morrow noted in presenting the MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST Elevation Acute Coronary Syndrome–Thrombolysis in MI) results at the annual meeting of the American College of Cardiology.

Those concerns have focused on the fact that ranolazine (Ranexa) is associated with a roughly 5-millisecond prolongation of the QT interval at the doses used in chronic angina.

Yet animal studies paradoxically suggest the drug suppresses markers of proarrhythmia, and the labeling warning concedes that "the clinical significance of the QT prolongation in the case of ranolazine is unknown."

In MERLIN, ranolazine showed no increase over placebo in all-cause or sudden cardiac death, and the drug actually reduced clinically significant arrhythmias on Holter monitoring, said Dr. Morrow of Brigham and Women's Hospital, Boston.

The MERLIN trial had three objectives. One was to provide additional safety information to guide clinical use of ranolazine. Another objective of the trial was to study the efficacy of the drug as an antianginal agent in a far broader patient population than had previously been studied—and ranolazine did significantly reduce severe recurrent ischemia, with a 1-year incidence of 13.9%, compared with 16.1% for placebo. There was a 23% reduction in the rate of worsening angina and a 19% decrease in need for intensification of antianginal therapy in the ranolazine group. The drug's antianginal effects were consistent regardless of whether or not the patients underwent coronary revascularization.

The incidence of clinically significant arrhythmia was 83.1% with placebo and 73.7% with ranolazine, for a significant 11% relative risk reduction.

The third aim of the trial was to determine if ranolazine reduces major cardiovascular events in patients with ACS or when used as secondary preventive therapy in patients with chronic stable angina. This was an attempt by the study sponsor, CV Therapeutics, to grab the brass ring by creating a major new indication for the drug.

On this score, the trial was negative; the 1-year rate of cardiovascular death or MI was 10.4% with ranolazine compared with 10.5% with placebo.

"This is not a disease-modifying drug," Dr. Morrow concluded.

Those who participated in the MERLIN trial had to have unstable angina or non–ST elevation MI plus one or more indicators of moderate to high risk of recurrent ischemic events or death.

About 24 hours after chest pain onset, the participants were randomized in double-blind fashion to intravenous ranolazine or placebo for up to 96 hours, followed by oral ranolazine at 1,000 mg b.i.d. or placebo for 1 year. The enrollees had extremely high rates of evidence-based background medical therapy. They were on Holter monitoring for the first 7 days to evaluate safety.

At 1 year, there were 65 sudden cardiac deaths in the placebo arm and 56 in the ranolazine group. The incidence of clinically significant arrhythmia on Holter monitoring—which was defined as ventricular tachycardia, new-onset atrial fibrillation, supraventricular tachycardia, complete heart block, bradycardia, or a greater than 2.5-second pause—was 83.1% with placebo and 73.7% with ranolazine, for a significant 11% relative risk reduction. All of the individual components of the Holter arrhythmia end point favored ranolazine, and the reduction in ventricular tachycardia reached statistical significance.

Dr. Morrow said the finding "warrants additional investigation for a new potential clinical application."

Cardiovascular Therapeutics announced MERLIN supports expansion of the existing ranolazine indication to include first-line antianginal therapy based upon a special protocol agreement the company made with the Food and Drug Administration in carrying out the trial.

Ranolazine is the most recently approved antianginal agent. It is unique in that its antianginal and anti-ischemic effects occur without having any clinically significant impact on heart rate or blood pressure. Its novel mechanism of action involves inhibition of the late sodium current. ■

FDA Panel Rejects Implantable Monitor for Heart Failure

BY ELIZABETH MECHCATIE
Senior Writer

GAITHERSBURG, MD. — A federal advisory panel recommended against approval of an implantable device that continuously measures intracardiac pressures in ambulatory patients with moderate to advanced heart failure, but panel members were enthusiastic about its potential and urged the manufacturer to continue studying the device.

At a meeting last month, the Food and Drug Administration's Circulatory System Devices Panel voted 9-2 that the Chronicle Implantable Hemodynamic Monitoring (IHM) System was "nonapprovable."

The manufacturer, Medtronic, had proposed that it be approved for the chronic management of patients with moderate to advanced heart failure in New York Heart Association class III or IV to reduce hospitalizations for worsening heart failure in these patients.

Although panelists generally agreed that intuitively, the technology made sense and provided useful information, they voted against approval because the COMPASS-HF study, the clinical trial submitted for approval, did not meet the primary effectiveness end point of showing that it reduced the rate of heart failure hospitalization equivalents (HF-related hospitalizations, HF-related emergency department or urgent-clinic visits requiring intravenous therapy) in patients with NYHA III or IV heart failure. And while the study provided reasonable assurance that the device was safe, panelists also cited the potential risks of an implantable device, with no effectiveness data to counterbalance the potential risks.

Panelist Dr. John Teerlink, director of heart failure at San Francisco Veterans Affairs Medical Center, described the technology as "tantalizing," but said that there was no evidence that it reduced patient hospitalizations for worsening heart failure.

This is a "lifelong implant, with certain known risks" and unknown risks that may occur with time, said panelist Dr. Jeffrey Borer, head of the division of cardiovascular pathophysiology, at the New York–Presbyterian Hospital. While he believed that the device accurately measured pressures that he believed were physically and pathophysiologically relevant.

"I haven't seen the data that tell me how to apply this information for predictable clinical benefit," Dr. Borer said.

The two panelists favoring approval thought that the device could be approved, but restricted to a very select population of heart failure patients.

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The Chronicle IHM system includes the hemodynamic monitor, the size and shape of a pacemaker, that is implanted into the upper chest, with a pressure sensing lead that is inserted into the right ventricle.

The system measures and stores data on right ventricular systolic and diastolic pressures, and estimated pulmonary artery diastolic pressure, as well as heart rate, core temperature, and patient activity, information that is transmitted by the patient remotely to the clinician, who can access the data via a Web site.

The COMPASS HF multicenter study enrolled 274 patients with NYHA class III (84%-87% of the patients) or IV heart failure, whose mean age was 58, who had been on standard medical therapy for at least 3 months, and had at least one HF-related hospitalization or emergency department visit that required intravenous treatment within the previous 6 months. The device was implanted in all patients, but clinicians had no access to the information in 140 patients, who served as the controls.

The rate of heart failure hospitalization equivalents through 6 months, the primary effectiveness end point, was 21% lower in the Chronicle arm, which was not statistically significant: 44 patients in the Chronicle arm had 84 HF-related hospitalization equivalents, (an event rate of 0.67 over 6 months), compared with 60 patients in the control group who had 113 HF-related events, an event rate of 0.85. Events in both groups were mostly hospitalizations.

Clinicians made nearly three times as many adjustments of medications in the CHRONICLE patients, with no evidence of complications associated with overdiuresis, according to Medtronic.

The panel agreed there was reasonable assurance that the device was safe. Almost 92% of patients had no system-related complications over 6 months, and there were no cases of pressure sensor failures.

Of the 277 attempted implants (3 were not successful), there were 24 complications in 23 patients, most frequently lead dislodgement.

Panelists encouraged Medtronic to continue studying the device.

The FDA usually follows the recommendations of its expert advisory panels, which are not binding. In a statement issued after the meeting, Dr. David Steinhaus, medical director of cardiac disease management at Medtronic, said that the company was committed to making the Chronicle IHM available worldwide to heart failure patients and plans to work closely with the FDA to "define the appropriate path for approval." ■