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EDITORIAL COMMENT

Cardiac Myosin Activators for the Treatment of Heart Failure

Stop Now or Push Ahead?*

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The ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) trial, in this issue of the *Journal*, was designed as a phase II investigation to determine the safety of intravenous omecamtiv mecarbil (OM) in patients admitted to the hospital with acute systolic heart failure (HF) (1). The primary efficacy endpoint examined dyspnea during the hospitalization. Subjects received a 48-h infusion of OM or placebo, and 3 cohorts were consecutively enrolled with escalating doses of OM. The dyspnea endpoint was intricate: dyspnea was measured at multiple time points and required an improvement at 6 h as a contingency to assess subsequent time points at 24 and 48 h and freedom from worsening HF or death from any cause at 48 h. Key inclusion criteria for enrollment included ejection fraction ≤40%, elevated natriuretic peptide level, and persistent dyspnea 2 h after receiving at least 40 mg of intravenous furosemide (or equivalent).

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In 606 patients, OM did not improve the primary efficacy endpoint of dyspnea relief or any of the secondary outcomes. The authors concluded that OM was "generally well-tolerated, increased systolic ejection time, and may have improved dyspnea in the high-dose group." Furthermore, the authors state that ATOMIC-HF provides the basis for additional investigation of intravenous OM for the treatment of acute decompensated HF and oral OM for the treatment of chronic HF. The question for commentary is whether OM warrants further development, acknowledging that ATOMIC-HF was a negative phase II trial.

ATOMIC-HF DESIGN

This was a well-designed phase II clinical trial. Dyspnea is a complex endpoint and has been shown to be related to markers of volume overload and pulmonary congestion (2,3). It is not surprising in this relatively small study that the primary endpoint was not met. Nesiritide failed to reach the primary efficacy endpoint for dyspnea in a similar patient population in a trial of more than 7,000 patients (4). The investigators gambled, as dyspnea is a very challenging endpoint, but is nonetheless very relevant to congested HF patients and necessary to evaluate. The relief of dyspnea trends was neutral, although it pointed in a positive direction in cohort 3, which received the highest dose of OM. Numerous very important secondary and safety endpoints were examined. An echocardiography substudy was conducted to assess standard indexes of left ventricular (LV) systolic function, including ejection fraction, fractional shortening, volumes, and systolic ejection time (SET). The investigators reported that SET was increased in subjects receiving OM in a dose-dependent manner; importantly, however, only 89 subjects of the planned echocardiography cohort of 240 had echocardiography measurements completed.

PHYSIOLOGICAL PROPERTIES OF OM

In normal male volunteers, OM demonstrated a provocative pharmacological property: it has the ability

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to augment LV systolic function (5). OM is a cardiac myosin activator that prolongs systolic ejection time, which is decreased in patients with reduced ejection fraction and further reduced both by positive inotropic agents (e.g., dobutamine and milrinone) and beta-blockers. A balance between systolic ejection time and diastole is important to provide diastolic coronary blood flow, which is also related to LV end-diastolic pressure and heart rate. The interplay is physiologically complex but is relevant, as myocardial ischemia was reported at plasma concentrations of OM in excess of 1,200 ng/ml in healthy volunteers (5). The ATOMIC-HF investigators cautiously monitored troponin and plasma concentrations of OM. In cohort 3, which received the highest dose of OM, the change in troponin I comparing baseline and 48 h was 0.001 ng/ml versus −0.005 ng/ml placebo. Plasma levels of OM in cohort 3 at 48 h were 425 ± 173 ng/ml. Rates of serious adverse events were similar in both groups, and the authors stated that definitive conclusions regarding the "small magnitude of the troponin change could not be made."

The response of HF patients to OM, with respect to myocardial ischemia versus healthy volunteers, should be viewed with caution. Coronary blood flow is affected by many variables in patients with HF. The potential efficacy of OM might be defined by a narrow, concentration-dependent (plasma levels) therapeutic window defining risk (ischemia) versus benefit. The signals of potential clinical benefit of OM in systolic HF are numerous, including reduced LV volumes, increased stroke volume, and reduced heart rate, and this is achieved without associated hypotension or arrhythmias.

FUTURE DIRECTIONS

Although controversial, markers of reverse remodeling have been heralded as surrogate endpoints indicative of reductions in mortality (6). The search for safe inotropic agents has been a continuing journey over the past 2 decades (7,8). The sobering fact is that we still do not understand the fundamental mechanisms that are responsible for the progression of HF (9). Respected clinical scientists usually only rely on hypotheses to justify the significance of clinical observations in carefully designed phase I and II investigations to plan future development and phase III clinical trials.

Approval of OM for intravenous use in the treatment of acute systolic HF will require a sizeable phase III randomized controlled clinical trial. All-cause mortality at 180 days was 12.5% in OM and 12.9% in placebo. Serelaxin is currently being evaluated in the RELAX-AHF (RELAXin in Acute Heart Failure 2) trial with a study population similar to ATOMIC-HF and with a 180-day cardiovascular mortality endpoint; planned enrollment is 6,800 subjects (10,11). The complexity and cost of a phase III trial for intravenous OM is likely prohibitive. The narrow therapeutic window, potential differential efficacy on the basis of etiology of HF, and concern for myocardial ischemia all may limit enthusiasm for a phase III trial.

A phase II clinical trial of oral OM in chronic systolic HF, COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure; NCT01786512), completed enrollment (n = 544) in August 2015. More insight will be gained regarding the pharmacokinetics of oral OM and its relationship to systolic ejection times. Results of COSMIC-HF will surely determine the future development of OM in chronic systolic HF. The recent PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor-Neprilysin Inhibitor] with ACEI [Angiotensin-Converting-Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial) comparing valsartan/sacubitril versus enalapril in chronic systolic HF showed a marked reduction in mortality but required a global clinical trial with enrollment of more than 8,400 patients (12). Valsartan/sacubitril is a newly approved agent, which is designated as an angiotensin receptor neprilysin inhibitor. Any new drug seeking a reduction in mortality will need to be compared to optimal medical therapy, which will include angiotensin receptor neprilysin inhibitors, beta-blockers, and mineralocorticoid inhibitors.

OM is a unique pharmacological agent defined as a myosin activator. OM should not be considered as a positive inotropic agent, which tends to decrease SET; indeed, OM increases SET, which may represent a novel and efficacious physiological target for systolic HF. The findings from ATOMIC-HF provide further proof of concept that OM may provide clinical benefit for HF with reduced ejection fraction. For now, caution is advised; more knowledge from the COSMIC-HF trial may clarify the potential role of OM in the treatment of HF.

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