心不全患者において心筋ミオシン活性化因子は収縮能を増加させる

ATOMIC-AHF：一次有効性エンドポイントは逃したが、omecamtiv mecarbilの好ましい傾向が認められた

ATOMIC-AHF: Despite missing primary efficacy endpoint, positive trends identified for omecamtiv mercabil

心筋ミオシン活性化因子omecamtiv mecarbil（OM）は急性心不全患者の呼吸困難軽減における一次有効性エンドポイントは達成できなかったとの第2相ATOMIC-AHF（Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure）スタディが2013年European Society of Cardiology学会で発表された。しかし、最大用量を投与されたコホートでは呼吸困難の改善が大であり、用量および濃度依存性のその他の好ましい傾向が認められた。研究者らは安静時または軽労作時呼吸困難を伴い緊急入院した左室収縮障害患者613人を、プラセボまたは血漿濃度を115、230、および310ng/mLと増加させる3つの用量のOMを48時間静脈内投与する群に無作為に割り付けた。蓄積されたプラセボ群と比較し、OM群は呼吸困難症状において差はなかった（*P*=0.33）。しかし、最大用量のOM群では対照のプラセボ群よりも有効性が高い傾向にあり（51%対37%、*P*=0.03）、有効性は有意に用量依存的および血漿濃度依存的な傾向であった（それぞれ*P*=0.025および*P*=0.007）。さらに、収縮期駆出時間も有意に濃度依存的に増加した（*P*<0.001）。また、心不全増悪は軽減し、上室性不整脈発現は減少し、心室性不整脈は増加しない傾向も認められた。

Full Text

Omecamtiv mecarbil, a cardiac myosin-activator, did not achieve its primary efficacy endpoint in reducing dyspnea in patients with acute heart failure, according to the results of the phase II ATOMIC-AHF (Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) study.

However, a cohort which received the highest dose of the drug showed greater dyspnea relief compared with placebo, and there were also other favorable dose and concentration-related trends, noted lead investigator John R. Teerlink, M.D., Professor of Clinical Medicine at the University of California San Francisco and Director of Heart Failure at the San Francisco Veterans Affairs Medical Center, USA.

"The study was a real success for its purpose, as a dose-finding, safety and tolerability study," he said. "The main objective of ATOMIC-AHF was to investigate the pharmacokinetics and tolerability of intravenous omecamtiv mecarbil in the acute heart failure (AHF) population, and like most Phase II studies, it was not powered or designed around the efficacy endpoint," he explained.

"We are pleased to see as much efficacy signal as was apparent, and the study provides essential data to inform the dosing regimen for future Phase 3 trials of the intravenous formulation."

ATOMIC-AHF enrolled 613 patients with left ventricular systolic dysfunction who were acutely hospitalized with dyspnea at rest or minimal exertion.

The subjects, from 106 sites in North America, Europe and Australia, were randomly assigned to receive 48 hours of intravenous placebo or omecamtiv mecarbil (OM) in 3 ascending dose cohorts designed to achieve plasma concentrations of 115, 230, and 310 ng/mL.

The primary efficacy endpoint was the effect on dyspnea at 6, 24 and 48 hours, with secondary endpoints of safety, tolerability, pharmacokinetics, and echocardiographic indices of cardiac function.

Compared to the pooled placebo groups the OM groups showed no statistically significant difference in dyspnea symptoms (*P* = 0.33) - therefore, the primary endpoint was not met, said Prof. Teerlink. However, in the cohort with the highest OM dose there was a trend towards greater response compared to its paired placebo group (51% vs. 37%, *P* = 0.03), along with significant dose-related and plasma concentration-related trends in response (*P* = 0.025 and *P* = 0.007, respectively).

Additionally, there were significant (P < 0.001) concentration-related increases in systolic ejection time, which is the echocardiographic signature of OM, said Prof. Teerlink.

"Unlike prior agents that increased intracellular cAMP and calcium and decrease ejection time, omecamtiv mecarbil's unique mechanism of action prolongs ejection time, allowing for increased stroke volume without significantly increased myocardial oxygen consumption," he said. "This effect has been remarkably reproducible from healthy dogs, dogs with heart failure, healthy human volunteers, and patients with both chronic, and now in ATOMIC-AHF, acute heart failure."

As seen in previous studies, OM produced significant reductions in heart rate (*P* < 0.001) without decreasing systolic blood pressure, said Prof. Teerlink.

There were also trends toward reductions in worsening heart failure, reduced incidence of supraventricular arrhythmias, and no increase in ventricular arrhythmias.

"None of these outcomes should be considered confirmed, since that was not the intent of the study, but the trends are very encouraging, especially for a trial of its size and scope," he said, adding that adverse events, including adjudicated deaths and rehospitalizations were "indistinguishable" from placebo.

There were 7 post-randomization myocardial infarctions in the omecamtiv mecarbil treated groups compared with 3 in placebo treated groups (2.3% vs. 1.0% respectively). There was a modest increase in cardiac troponin I in OM-treated patients, but no evidence to suggest this was linked to increasing OM concentrations, "however, we will be vigilant about studying the ATOMIC-AHF data for possible explanations."

"One of the greatest challenges of the ATOMIC-AHF trial has been managing expectations, explained Prof. Teerlink. "Omecamtiv mecarbil is probably one of the most interesting new chemical entities in cardiovascular medicine now and consequently, expectations are very high in the scientific and lay communities. Physicians have struggled for decades to develop agents that improve cardiac function without increasing arrhythmias or mortality; omecamtiv mecarbil has the potential to be such an agent."

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Unlabeled/unapproved uses disclosure: Use of omecamtiv mecarbil in patients with heart failure is investigational.

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