Serelaxin: Insights into its haemodynamic, biochemical and clinical effects in acute heart failure

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Treatment for acute heart failure (AHF) has not changed much in the last two decades. Intravenous drugs such as levosimendan, nesiritide, rolofylline and tezosentan have been studied in phase III randomized controlled trials (RCTs) with disappointing results. None of these drugs improved dyspnoea, worsening heart failure, readmissions to the hospital, cardiovascular mortality or all-cause mortality in AHF patients, mostly in the short-term follow-up. These drugs increased the probability of ventricular and atrial arrhythmias or symptomatic hypotension (levosimendan, nesiritide), or seizures and strokes (rolofylline). Ularitide, a novel natriuretic peptide, is undergoing a phase III RCT focused on symptoms and cardiovascular mortality. Several reasons for negative results are possible, including high heterogeneity of patients with AHF, several sources of bias in RCTs, scarcity of outcomes, and incomplete pre-clinical evaluation of drugs.

Serelaxin, a recombinant human relaxin-2 peptide, regulates maternal adaptations to pregnancy, including arterial vasodilation, increased cardiac output and increased renal blood flow. Given its potential for the treatment of AHF, this drug has been tested in phase II (Pre-RELAX-AHF) and
phase III (RELAX-AHF) RCTs. These trials aimed to improve the design issues of other intravenous drugs for AHF. In the dose-finding Pre-RELAX-AHF trial, 234 patients with AHF, dyspnoea, congestion on chest X-ray, increased brain natriuretic peptide (BNP) or NT-terminal prohormone of BNP (NT-proBNP), mild to moderate renal insufficiency and systolic blood pressure (SBP)>125 mmHg received 48-h intravenous infusion of serelaxin vs. placebo. Authors felt these patients had more chances to get benefit from serelaxin, with lower chances of harmful effects. Indeed, they found improvements of dyspnoea (as measure by a visual analogue scale or Likert score), worsening of heart failure, cardiovascular death or readmission to hospital due to HF or renal failure at 60 days, and cardiovascular mortality at 180 days, especially with the 30 μg/kg per day dose.

The phase III RELAX-AHF trial involved 1161 patients with similar inclusion and exclusion criteria as the Pre-RELAX-AHF trial. Authors also used the same methodology to measure the primary outcome dyspnoea, the 30 μg/kg per day dose vs. placebo, the same time of serelaxin infusion, and analysed an intention-to-treat (ITT) population. They found a mild decrease in dyspnoea, and decrease on early worsening HF, congestion, initial length of hospital stay, duration of intensive care, cardiovascular death at 180 days, and all-cause mortality at 180 days. There was no difference vs. placebo in days out of hospital at 60 days, cardiovascular death or readmission to hospital due to HF or renal failure at 60 days. Taking together, the results of the RELAX-AHF trial were in the positive direction and promising.

However, the mechanisms of these favourable effects have not been fully elucidated. Metra et al. used data from the RELAX-AHF trial and found that biomarkers of cardiac (high sensitive cardiac troponin T [hs-cTnT]), renal (cystatin-C) and hepatic (aspartate transaminase and alanine transaminase) damage and decongestion (NT-proBNP) at day 2 and worsening HF were associated with the all-cause mortality at 180 days. Serelaxin diminished these biomarkers, which may be a sign
of prevention of organ damage and quicker decongestion process. The haemodynamic effects of serelaxin in AHF have not been evaluated in the RELAX-AHF trials or in other studies, and a better understanding of these effects can give a better picture of the mechanisms associated with improved symptoms and clinical outcomes.

In this issue of the Journal, Ponikowski et al. report the results of an RCT of 71 patients (mean age: 69 years-old) with dyspnoea at rest or minimal exertion and pulmonary congestion, non-electively admitted-required to hospital for AHF management, with pulmonary capillary wedge pressure (PCWP) ≥18 mmHg, SBP ≥115 mmHg (mean SBP at baseline: 131 mmHg) and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m² (mean eGFR at baseline: 70). Within 48h of hospitalisation, serelaxin was given ina 20h-infusion at 30 μg/kg per day vs. placebo. There was a small decrease (-2.4 mmHg vs. placebo) in peak changes from baseline of PCWP during the first 8h, without changes of cardiac index (CI) levels. During the 24h infusion, it was observed significant decreases in systolic and diastolic pulmonary artery pressure (PAP), right atrial pressure (RAP), and pulmonary vascular resistance (PVR), as well as slight decreases of systemic vascular resistance (SVR), SBP, and diastolic BP (DBP). No changes in heart rate were seen. In agreement with the RELAX-AHF trial, creatinine clearance increased and NT-proBNP decreased vs. placebo.

Hypotension and syncope were uncommon and not different from placebo. This RCT expands our understanding of the effects of serelaxin and the pathophysiology of AHF (Figure).

Vasoconstriction is a major factor in the pathophysiology of AHF. Serelaxin demonstrates in this RCT a short-term decrease in PAP and RAP and a posterior decrease in PCWP suggesting a precapillary and capillary vasodilation, respectively, that relate to improvement of dyspnoea and decongestion. Importantly, there was a slight decrease in BP and SVR, which helps explain the scarcity of harmful hypotension events. Other RCTs have evaluated the effects of vasodilators on PCWP, but in younger populations and with lower SBP levels than the Ponikowski et al. and
RELAX-AHF trials. In the VMAC trial, the recombinant BNP nesiritide in comparison to placebo decreased by 3.8 mmHg the PCWP at 3h of infusion. These patients had AHF, dyspnoea and congestion, a mean age 62 years-old, and mean SBP at baseline of 120 mmHg. In the SIRIUS II trial, the natriuretic peptide ularatide in comparison to placebo decreased by 6 mmHg the PCWP at 6h of infusion of the two highest doses; patients had decompensated HF and dyspnoea, a mean age of 60 years-old, and mean SBP at baseline of 126 mm Hg.

The key question is whether these short-term haemodynamic changes are associated or not with long-term clinical outcomes. The decrease in all-cause mortality at 180 days in the RELAX-AHF trial has not been associated with decreased readmission to the hospital. In fact, reduction in readmission to the hospital has not been demonstrated in all other drugs for AHF. The small number of deaths made the reduction in mortality not a confident finding. So, even the significant mortality reductions should be taken carefully. In the ASCEND-AHF population with median SBP at baseline of 120 mmHg and otherwise similar population to the RELAX-AHF trial but older population (median age 67 years-old) than the VMAC trial, O'Connor et al. found that nesiritide vs. placebo did not reduce rehospitalisation for HF, all-cause mortality or cardiovascular mortality at 30 days.

How confident are we on the findings of the Ponikowski et al. trial? This was a small, phase II RCT. The randomization procedure and the blinding of patients, health-workers and study personnel were appropriate; patients were similar at baseline. The primary analysis was per-protocol, although ITT analysis gave similar results in sensitivity analysis. Per-protocol analysis exaggerates treatment effects, and therefore the conservative ITT analysis is preferred in superiority RCTs. Five patients on placebo received unplanned furosemide in comparison to one patient on serelaxin; given the small sample, patients were therefore not equally treated. Also, will the results help me in caring for my patients? Haemodynamic outcomes were the only focus of this trial. Main haemodynamic outcomes were appropriately chosen. Results of this RCT are applicable to the subpopulation of AHF patients.
with SBP≥115 mmHg and eGFR≥30 mL/min/1.73m². Hypotension and syncope were similar to the placebo group, so it appears that there are no safety problems. Finally, cost information and cost-effectiveness analyses will give a better picture on the usefulness of serelaxin in clinical practice. How would serelaxin work in different subgroups of AHF patients? A recent publication of the RELAX-AHF Investigators\(^\text{13}\) has shown that dyspnoea relief and cardiovascular death and rehospitalisation due to HF or renal failure at 60 days were consistent across subgroups. Cardiovascular mortality and all-cause mortality at 180 days, however, showed some significant differential effects across subgroups. These findings should be taken with caution given the large number of subgroups studied, the low power of the interaction test used, and the scarcity of death in some significant subgroups.\(^\text{14}\) Results from the RELAX-AHF-2 trial, specifically designed to evaluate the effects of serelaxin on mortality, will clarify this issue.

Serelaxin is a promising drug for the treatment of AHF, with several positive haemodynamic, biochemical and clinical effects in patients with dyspnoea, congestion, normal to high SBP and mild to moderate renal insufficiency. In June 2013, the Food and Drug Administration (FDA) granted Breakthrough Therapy designation to serelaxin\(^\text{15}\) and likely this drug will have a faster review process.

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