Serelaxin, a ‘Breakthrough’ Investigational Intravenous Agent for Acute Heart Failure

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INTRODUCTION

Heart failure (HF) is a complex clinical syndrome resulting from any structural or functional impairment of ventricular filling or ejection of blood. The most common manifestations include dyspnea, fatigue, and fluid retention. Approximately 3% of Americans have HF, and the prevalence exceeds 10% in patients older than 70 years of age. HF is responsible for significant morbidity and mortality within the U.S. In addition, the direct treatment cost associated with HF is projected to reach $32.4 billion by the year 2015.

Acute HF is the most common cause of hospitalizations in patients older than 65 years of age. The estimated mortality rate approaches 40% within the first year following hospitalization. In contrast to the successes of therapy for chronic heart failure, such as beta blockers and angiotensin-converting enzyme (ACE) inhibitors, the last 30 years have seen little improvement in the treatment of acute HF.

Treatment of acute HF currently centers on the administration of diuretics in combination with fluid and sodium restriction. Although initial treatment with diuretic therapy provides symptomatic relief, data are lacking to support a mortality benefit in such patients. Many patients also remain symptomatic at 24 hours, and nearly 25% of patients experience a worsening of symptoms during their inpatient stay.

In addition to diuretics, vasodilators (including nitroglycerin and nitroprusside) may be used to treat episodes of acute HF. It is thought that vasodilator therapy in patients with preserved systolic function, hypertension, or both, might be more beneficial than diuretics. However, large placebo-controlled, prospective randomized studies, powered to assess the benefit and safety of such vasodilators in this setting, have been lacking. Most recently, in the ASCEND–HF trial (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure), the vasodilator nesiritide (e.g., Natrecor, Janssen) failed to provide dyspnea relief, to reduce all-cause mortality, or to improve renal function.

Finally, vasodilatory inotropes such as milrinone (e.g., Primacor, Sanofi) have been postulated to be beneficial in acute HF; however, evidence supporting this practice is lacking. It has also been theorized that acute HF exacerbations and the therapeutic interventions involved in the care of such exacerbations may lead to disease progression via increased inflammatory and neurohormonal activation, hemodynamic compromise, and eventual end-organ damage. The shortcomings of the aforementioned approaches have prompted researchers to seek novel therapeutic alternatives that can inhibit the activation of such factors and improve patient outcomes in the acute-treatment setting.

In the quest to advance the treatment of acute HF, researchers have identified relaxin as a potential target. Relaxin is a naturally occurring peptide that is produced by the corpus luteum. During pregnancy and birth, relaxin concentrations rise. Increased levels of relaxin result in improved arterial compliance and cardiac output with enhanced renal blood flow via dilation of afferent and efferent arterioles.

In a small dose-ranging study, the administration of relaxin to patients with chronic HF yielded promising hemodynamic and neurohormonal effects. In view of these results, relaxin has become an attractive potential agent for the treatment of acute HF.

PHARMACOLOGY

Serelaxin (RLX030, Novartis) is a recombinant form of human relaxin-2, a naturally occurring peptide. It exerts its effects by binding to one of two receptors, LGR7 and LGR8, to activate a G protein–coupled receptor pathway on endothelial cells of the vasculature. Receptor binding activates and upregulates the vascular endothelin B receptor, vascular endothelial growth factor (VEGF), and nitric oxide production. This process results in decreased systemic vascular resistance, increased cardiac output, increased renal blood flow, and an increased glomerular filtration rate (GFR).

Serelaxin is also thought to inhibit angiotensin II and endothelin, thereby causing further systemic and renal vasodilation. In contrast to targeted therapy with vasodilators and inotropes, the multifaceted, indirect effects of serelaxin on the hemodynamic profile may make it a valuable option in the treatment of acute HF, a complex disease.

The structural formula for serelaxin is shown in Figure 1. The molecular formula is C146H208N74O74S8, and the molecular weight is 5.96 kilodaltons.
PHARMACOKINETICS

Although the pharmacokinetic properties of serelaxin have not been studied in patients with acute HF, a substantial amount of data describes the pharmacokinetics of serelaxin in the treatment of scleroderma. Serelaxin is administered as a continuous intravenous (IV) infusion over a period of 24 to 48 hours. At doses of less than 200 mcg/kg/day, plasma steady-state concentrations exhibit proportional increases with increasing dosage. Serelaxin demonstrates linear clearance in dosages of 100 mcg/kg/day or less, with clearance decreasing and becoming nonlinear at higher dosages. When the drug is administered at dosages of 6, 12, 50, and 100 mcg/kg/day, its half-life averages 5.28 days.23

CLINICAL TRIALS

Phase 1, Dschietzig et al.18,21

A single-center, open-label dose-escalation study was conducted in 16 compensated, stable patients with HF to evaluate the safety, tolerability, and pharmacodynamics of IV recombinant human relaxin (serelaxin). Patients were older than 18 years of age. Hemodynamic and neurohumoral endpoints were measured. Left ventricular ejection fraction in these patients was less than 35%. Patients were receiving chronic HF treatment, including ACE inhibitors or angiotensin receptor blockers (ARBs), beta blockers, diuretics, and antiplatelet agents.

Patients were successively assigned to three dose-escalating cohorts of IV relaxin. Four patients in group A received infusions over a period of 8 hours at doses of 10, 30, and 100 mcg/kg/day. After safety and tolerability were confirmed, six patients in group B received infusions, each with doses of 240, 480, and 960 mcg/kg/day, over a period of 8 hours. Subsequently, six distinct patients in group C received the highest tolerated safe dose, equivalent to 960 mcg/kg/day for 24 hours.

Relaxin generated trends expected with vasodilation—increases in the cardiac index, decreases in pulmonary capillary wedge pressure, systemic vascular resistance, and N-terminal prohormone of brain natriuretic peptide (NT-pro BNP). These effects lasted for a minimum of 8 hours after the infusion was discontinued, and no associated hypotension was observed. Although creatinine and blood urea nitrogen levels were improved, the 960-mcg/kg/day regimen produced a nonsignificant transient increase in these markers.

This was the first study to evaluate relaxin in patients with stable HF. The drug was considered a safe, tolerable treatment option, producing pharmacodynamic effects that were suggestive of vasodilation without significant hypotension. Results from this prospective pilot trial provided the impetus for further studies to evaluate the effects of relaxin in patients with uncompensated HF.

Phase 2, Teerlink et al.24

Symptom relief, safety, and other clinical outcomes were evaluated in a randomized, placebo-controlled, parallel-group, dose-ranging, double-blind multicenter study involving patients 18 years of age and older. Patients with the following characteristics were enrolled within 16 hours of presentation: acute HF; dyspnea; congestion; increased levels of BNP or NT-pro BNP; mild-to-moderate renal insufficiency (i.e., GFR, 30–75 mL/min/1.73 m2); and systolic blood pressure (BP) above 125 mm Hg. Although dyspnea was assessed via a 7-point Likert scale and a 100-mm Visual Analogue Scale (VAS), the main objective of the trial was to identify a dose of relaxin that demonstrated both safety and efficacy with predetermined clinical outcomes.

At the discretion of the clinician, patients received standard care and an IV infusion of either placebo or relaxin 10 mcg/kg (n = 40), 30 mcg/kg (n = 43), 100 mcg/kg (n = 39), or 250 mcg/kg (n = 50) daily for 48 hours. Patients were considered to be candidates for therapy after receiving a minimum of 40 mg of IV furosemide (e.g., Lasix, Sanofi-Aventis) or an equivalent dose of an alternative loop diuretic if they were not receiving IV inotropic agents or IV vasodilators, other than IV nitrates, and only if systolic BP was higher than 150 mm Hg.

In the group receiving relaxin 30 mcg/kg/day, dyspnea (according to the Likert scale) significantly improved in 40% of patients at 6, 12, and 24 hours; in patients who received placebo, dyspnea improved in only 23% (P = 0.044). Dyspnea relief, according to the VAS, reflected a positive yet nonsignificant effect with relaxin. The mean hospital length of stay for patients treated with relaxin was 10.2 days compared with 12.0 days for the placebo patients. After 60 days, the number of cardiovascular deaths or readmissions secondary to heart failure or renal failure was decreased with relaxin compared with placebo (2.6% vs. 17.2%, respectively; P = 0.053).

Of the doses studied in this trial, relaxin 30 mcg/kg daily provided the most significant benefit in the majority of the predetermined clinical outcomes. Improvement was demonstrated in the relief of dyspnea, in cardiovascular death or 60-day readmission, and in cardiovascular death at 60 days. These positive results suggested that relaxin 30 mcg/kg/day was a dosing regimen that should be further evaluated in large, randomized clinical trials with one primary and one secondary endpoint.

Phase 3, Teerlink et al.20 and Ponikowski et al.25

Dyspnea relief, safety, tolerability, and clinical efficacy outcomes after hospital discharge were assessed in a prospective, randomized, double-blind, placebo-controlled, parallel-group trial to compare serelaxin with placebo in patients with acute HF. The same inclusion criteria were incorporated as in phase 2 (acute HF; dyspnea; congestion; elevated BNP or NT-pro BNP levels; mild-to-moderate renal insufficiency; GFR, 30–75 mL/min/1.73 m2; and systolic BP above 125 mm Hg).

Because the primary endpoint was improvement in dyspnea, the researchers used both the VAS and the area-under-the-curve (AUC) concentration to day 5, along with the Likert scale, to assess dyspnea improvement during day 1. Secondary outcomes included (1) days alive and out of hospital to 60 days and (2) cardiovascular death or readmission for HF or renal failure before 60 days.

Serelaxin 30 mcg/kg/day or placebo was administered to 567 and 570 patients, respectively, over a period of 48 hours. If systolic BP was reduced by more than 40 mm Hg but was higher than 100 mm Hg, patients received half the dose for the remainder of the 48 hours. If systolic BP declined to less than 100 mm Hg, if significant laboratory changes occurred, or if significant adverse events were experienced, serelaxin was discontinued.

According to the VAS and the AUC concentration, dyspnea was significantly
improved with serelaxin compared with placebo ($P = 0.007$). Patients experienced less dyspnea from 6 hours to day 5. Moderate or significant dyspnea improvement was not expressed with the Likert scale. There were no statistically significant differences between serelaxin and placebo when secondary outcomes were measured.

By day 2, serelaxin therapy led to more early reductions in signs and symptoms of congestion even without any changes from baseline body weight. Despite the lack of decreases in hospital readmission rates on day 30 or 60, length of stay was reduced by 0.9 days in patients who received serelaxin ($P = 0.04$). A statistically significant decline in cardiovascular death, as well as a decrease in all-cause mortality rates, was noted with serelaxin compared with placebo at 180 days ($P = 0.019$). Thirty-day all-cause mortality was similarly reduced, but statistical significance was not achieved.

Serelaxin improved dyspnea and reduced worsening heart failure events, signs and symptoms of congestion, length of stay, and time in intensive care.

Although serelaxin resulted in improved mortality rates at 180 days, the study was not powered to address this outcome. Another trial confirming this finding would be beneficial, because no previous medications for acute HF have been shown to reduce mortality rates after hospital discharge.

**ADVERSE DRUG REACTIONS**

**Phase 1, Dschietzig et al.$^{18,21}$**

Because no infusion-related significant adverse drug events were noted with escalating doses of relaxin (serelaxin), the highest dose used (i.e., 960 mcg/kg/day) was subsequently tested in six patients over a period of 24 hours. No consequent infusion-related adverse events were noted with this high-dose regimen.

Three weeks after the relaxin infusion was discontinued, one patient experienced angina pectoris requiring hospitalization. Angiographic evaluation revealed no progression of coronary artery disease. Seven additional adverse events occurred, but they were not attributed to the drug.

Vital signs, clinical status, electrocardiographic results, chemistry profiles, and hematological parameters were stable throughout the observation period.

**Phase 2, Teerlink et al.$^{24}$**

Two of the 36 hypotension-related adverse events that warranted discontinuing relaxin were considered serious and affected patients in the cohort receiving 250 mcg/kg/day. None of the patients experienced a drop in systolic BP below 80 mm Hg. After the relaxin infusion was discontinued, systolic BP increased or stabilized in most patients without treatment. In the groups receiving relaxin 10 or 30 mcg/kg/day, none of the patients required treatment for BP reduction.

Although there were no differences in serious adverse events secondary to renal failure, more persistent renal impairment was experienced with relaxin 250 mcg/kg/day versus placebo. This difference was not significant ($P = 0.19$). Electrolytes and liver function test results remained stable.

**Phase 3, Teerlink et al.$^{20}$**

After serelaxin was stopped, a decrease of 4 to 6 mm Hg in systolic BP from baseline was observed for up to 24 hours, compared with placebo. Serelaxin patients needed more dose adjustments than placebo patients because of BP reductions ($P = 0.0001$). These adjustments resulted in a 50% dose decrease, a discontinuation of the study drug, or both.

Although 12% of serelaxin patients, compared with 8% of placebo patients, required treatment to reduce BP (primarily with IV fluids), the remaining cases of hypertension resolved without intervention.

The placebo patients experienced a statistically significant increase in renal impairment compared with the serelaxin group ($P = 0.03$), but other adverse events between the two groups were similar. A reduction in mortality rates at 180 days was also noted.

**DRUG INTERACTIONS**

No drug–drug interactions have been reported with serelaxin, but patients were excluded from the trials if they were taking IV medications for HF.$^{20,24}$

**PRECAUTIONS AND WARNINGS**

Although data are limited in terms of the use of serelaxin, caution should be taken to exclude patients with low systolic BP because of the vasodilatory effects of this medication.

**ROLE OF SERELAXIN IN THERAPY**

The treatment of acute HF has traditionally involved targeted therapy consisting of diuretics, vasodilators, and inotropes. However, these agents have not shown significant benefits in clinical trials and they are associated with adverse effects.

Serelaxin’s multidimensional indirect mechanism on the hemodynamic profile and its minimal adverse effects should make it a useful agent in the treatment of acute HF. Upon FDA approval, if serelaxin is considered for formulary inclusion, related protocols should be developed with instructions for titrating and interrupting therapy as well as for incorporating biomarker data. Including patients with elevated systolic BP would be consistent with the design of the studies to help mitigate the potential for vasodilation-induced hypotension.

Patients with vasoconstriction, congestion (such as those receiving background loop diuretics), and mild-to-moderate renal impairment early in the course of an HF exacerbation are most likely to experience the beneficial actions conferred by this medication.

**CONCLUSION**

The FDA has granted a “breakthrough therapy” designation for serelaxin, a recombinant form of human relaxin-2, for acute HF. Introduced in 2012, this designation is intended to expedite the development and review of drugs for serious or life-threatening conditions. Preliminary clinical evidence must show that a drug may bring substantial improvement for at least one clinically significant endpoint over currently available therapy.

Results from clinical trials of serelaxin demonstrated reduced dyspnea, congestion, and length of stay, among other outcomes. A limitation, however, is the potential drop in BP secondary to the drug’s mechanism of action in causing 

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REFERENCES


