Rationale and Design of the Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patient Evaluation (THE BALANCE) Study

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Abstract

Hyponatremia is a common electrolyte disorder in patients with heart failure (HF) associated with cognitive dysfunction and increased mortality and rehospitalization rates. Loop diuretics worsen renal function, produce neurohormonal activation, and induce electrolyte imbalances. Lixivaptan is a selective, oral vasopressin V_2 -receptor antagonist that improves hyponatremia by promoting electrolyte-free aquaresis without significant side effects. The Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patient Evaluation (BALANCE) study is a randomized, double-blind, placebo-controlled, phase 3 trial designed to evaluate the effects of lixivaptan on serum sodium in patients hospitalized with worsening heart failure (target $N = 650$), signs of congestion and serum sodium concentrations <135 mEq/L. Other endpoints include assessment of dyspnea, body weight, cognitive function, and days of hospital-free survival. Patients are randomized 1:1 to lixivaptan or matching placebo for 60 days, with a 30-day safety follow-up. Doses of lixivaptan or placebo are adjusted based on serum sodium and volume status. Lixivaptan was shown to increase serum sodium and reduce body weight, without renal dysfunction or hypokalemia. BALANCE seeks to address unmet questions regarding the use of vasopressin antagonists including their effects on cognitive function and clinical outcomes in patients with hyponatremia and worsening heart failure. Clin Trans Sci 2010; Volume 3: 249–253

Keywords: hyponatremia, arginine vasopressin, heart failure

Introduction

Management of patients with acute decompensated heart failure (HF) and hyponatremia is challenging. Indeed, loop diuretics, the mainstay therapy in acute HF, achieve the necessary fluid removal, but are also known for their side effects and to lead to further electrolyte imbalances.¹

Defined as a serum sodium concentration of <135 mEq/L, hyponatremia is seen in more than 20% of patients hospitalized with heart failure.² In these patients, hyponatremia is an independent and significant predictor of mortality and HF-related morbidity as well as hospital readmission.^{2–4} An analysis of data from 48,612 heart failure patients enrolled in the OPTIMIZE-HF registry demonstrated that for each 3-mmol/L decrease in serum sodium concentration below 140 mmol/L, the risk of in-hospital mortality increased by 19.5% among all patients.² Although the association between hyponatremia and poor clinical outcomes is well documented, a causal link has not been established. Cognitive impairment frequently observed as clouded mental state, impaired mental status, confusion, lethargy, and fatigue is also common in patients with hyponatremia. However, it is unknown whether hyponatremia is associated with cognitive dysfunction in patients with heart failure and whether improvements in sodium concentrations would also result in improved cognition.⁵

The hyponatremia and fluid retention seen in patients with acute and chronic heart failure is due at least in part to elevated levels of arginine vasopressin (AVP).^{6–9} AVP secretion

is induced by changes in serum osmolality and by nonosmotic factors, including low cardiac output and low systemic blood pressure.^{10,11} Vasopressin promotes water retention by binding to vasopressin V_2 receptors located in the distal tubules of the nephron, which induces free water reabsorption by increasing the number of available aquaporin-2 water channels in the apical membrane of renal collecting duct cells.^{12,13} Thus, it is not surprising that a group of vasopressin receptor antagonists including conivaptan, lixivaptan, satavaptan, and tolvaptan have all demonstrated the ability to increase serum sodium levels in patients with hyponatremia.¹⁴

The V_2 -selective vasopressin antagonist tolvaptan has been evaluated in a series of clinical trials and is approved by the Food and Drug Administration for the treatment of hyponatremia. However, studies designed to assess the effects of tolvaptan in patients with hyponatremia included only 14 heart failure patients in a study by Gheorghiade et al.¹⁵ and 68 and 70 patients in the Salt 1 and Salt 2 studies, respectively.¹⁶ Investigators assessed the effects of three different doses of tolvaptan on change in body weight in 254 patients with left ventricular; however, only 70 of the patients had hyponatremia.¹⁷ More recently, in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) 4113 hospitalized with heart failure were randomized to 30 mg of tolvaptan or placebo—but only 318 patients had a serum sodium less than 134 mEq/L.^{18,19} Thus, there is considerable equipoise

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Key inclusion criteria	Key exclusion criteria
• Age ≥18 years	• Acute severe hyponatremia
• Baseline serum sodium concentration <135 mEq/L	• Symptomatic hyponatremia (e.g., severe lethargy, coma, seizures)
• Current hospitalization for worsening heart failure (i.e., requiring treatment for a minimum of 30 days prior to hospitalization)	• Uncontrolled (as defined by the investigator) diabetes mellitus
• Clinical evidence of volume overload with at least 2 of the following conditions: dyspnea, pulmonary congestion, peripheral edema, increased jugular venous pressure and/or hepatic congestion with ascites, baseline BNP ≥150 pg/mL or NT Pro-BNP ≥450 pg/mL	• Serum creatinine concentration >3.0 mg/day
• Documented LVEF within prior year	• Hemodynamically significant (per investigator) uncorrected primary cardiac valvular disease, hypertrophic cardiomyopathy, or congestive heart failure due to uncorrected thyroid disease, active myocarditis, or known amyloid cardiomyopathy
• Supine systolic arterial blood pressure ≥90 mm Hg	• Within prior 30 days
	- History of sustained ventricular tachycardia or ventricular fibrillation (except with automatic implantable cardioverter defibrillator)
	- History of stroke, cardiac revascularization procedure, or biventricular pacer placement
	- ST-segment elevation myocardial infarction
	• Active myocardial ischemia at the time of enrollment
	• Use of cardiac mechanical support
	• Planned revascularization procedures, electrophysiologic device implantation, cardiac mechanical support implantation, ultrafiltration or dialysis, cardiac transplantation, or other cardiac surgery within 30 days following study enrollment
	• History of primary significant liver disease or acute hepatic failure, as defined by the investigator
	• Comorbid condition with an expected survival of <6 months
	• Adrenal insufficiency
LVEF = left ventricular ejection fraction; BNP = brain natriuretic peptide; NT = N-terminal.	

Table 1. Key eligibility criteria.

as to the role of AVP antagonists in the treatment of patients with symptoms of heart failure and hyponatremia.

Lixivaptan is a selective, orally active, nonpeptide V₂-receptor antagonist²⁰ that has been previously shown to significantly increase solute-free water excretion, or aquaresis, in patients with chronic New York Heart Association (NYHA) functional class II or III systolic HF.²¹ We present the design of the THE BALANCE (Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patient Evaluation) study, a multicenter, double-blind, placebo-controlled phase 3 trial of lixivaptan in patients hospitalized with HF and hyponatremia. This study is designed to assess the efficacy of lixivaptan in the treatment of hyponatremia but will also address important questions that remain regarding the use of vasopressin antagonists in patients with heart failure by: enrolling only patients with hyponatremia; utilizing tailored therapeutic dosing rather than a single dose; assessing the effects of vasopressin antagonism on cognitive function; evaluating its use in patients with heart failure and preserved ejection fraction; and measuring the effects of the drug on a composite endpoint of hospital length of stay, readmission rate, and survival.

Study Design and Methods

Study overview

THE BALANCE study (clinicaltrials.gov identifier: NCT00578695) is being conducted internationally at approximately 300 clinical

centers. It is designed to assess the efficacy and safety of lixivaptan in achieving and maintaining increased serum sodium concentrations in patients who are hospitalized for worsening chronic HF with hyponatremia. Inclusion and exclusion criteria are detailed in Table 1. Randomization occurs after eligibility is confirmed and the diagnosis of hyponatremia is established. A total of 650 patients will be assigned to treatment with placebo or lixivaptan for up to 60 days, with posttreatment follow-up through day 90 (Figure 1). Concomitant standard therapy for HF, including the use of loop diuretics, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers and beta-blockers, is permitted. Prohibited medications include desmopressin; vasopressin or vasopressin analogs; vasopressin receptor antagonists; lithium; demeclocycline; nonselective calcium antagonists; and hypertonic saline. Use of these medicines or interventions may confound the interpretation of study results with regard to defining the specific impact of lixivaptan on hyponatremia.

Randomization and stratification

Patients are randomly assigned to treatment with lixivaptan or placebo at a ratio of 1:1. Random allocation will be stratified by serum sodium concentration at baseline (≥120 to <130 mEq/L [target $n \geq 200$] vs. ≥130 to <135 mEq/L) (Figure 1) and by country. A central randomization procedure based on an interactive voice response system is being used.

Figure 1. Overview of study design and treatments.

Treatment

Patients are assigned to receive oral lixivaptan (starting dose 50 mg once daily) or matching placebo within 48 hours of hospitalization. Lixivaptan doses will be titrated up to a maximum of 100 mg twice daily based on changes in serum sodium concentrations and volume status to achieve a slow correction of serum sodium over the first 3 days of treatment (Figure 1). Dose titration also is allowed between days 4 and 60 at the discretion of the investigator. Fluid restriction may be instituted, maintained, or adjusted at the discretion of the investigator at any time during the study.

Endpoints

Efficacy and safety endpoints are listed in Table 2. The primary study endpoint is the change from baseline in serum sodium concentrations at day 7 of treatment. Secondary study endpoints include the average area under the concentration-time curve of change from baseline in serum sodium concentrations up to day 60; the percentage of patients with worsening hyponatremia (a reduction of ≥ 3 mEq/L in serum sodium concentrations) during the treatment period; the percentage of patients with normalized serum sodium concentration (>135 mEq/L) at day 60; and days

of hospital-free survival (DHFS) during the treatment period (up to 60 days from randomization). DHFS is calculated by subtracting (from 60 days) the number of days the patient is hospitalized for cardiovascular causes and/or the patient is not alive during the planned 60-day treatment period. Cognitive impairment is assessed using the change from baseline in the time recorded for completion of the Trail Making Test, Part B (TMT-B) and the change from baseline in the Medical Outcomes Study-6 cognitive function scale (MOS-COG) at day 28. The TMT-B is a rater-administered, performance-based measure of a subject's cognitive functioning. It requires the subject to visually scan a page containing a pseudorandom arrangement of circles containing either numbers or letters and to quickly and flexibly alternate attention between the two sets of stimuli while connecting them in ascending sequence by drawing a continuous line with a pencil (i.e., 1-A-2-B-3-C...L-13). Performance on the test is measured in the total time it takes to sequentially connect the circles from beginning to end in the appropriate order. The MOS-COG instrument is a patient reported outcome measure.

Other endpoints include the change from baseline in body weight at day 2 (prior to day 2 dosing) and the change from baseline in patient-assessed dyspnea at 8 to 12 hours and at 24 hours from first dose. Safety endpoints include adverse events, vital signs, clinical laboratory tests, and 12-lead electrocardiograms.

Statistical considerations

A sample size of 125 patients in each group will have 98% power to detect a difference in serum sodium means at day 7 of 4.2 mEq/L (the difference between lixivaptan mean change from baseline of 5.2 mEq/L and placebo mean change from baseline of 1.0 mEq/L) assuming that the common standard deviation of changes is 8.23 using a 2-group *t*-test with a 0.05 two-sided significance level. Type III analysis in SAS® software will be used for treatment comparisons based on an analysis of covariance model with treatment, country, and baseline sodium level (<130 mEq/L vs. ≥ 130 mEq/L) as factors and baseline sodium value as covariate.

Endpoint	Type	Category
Change from baseline in serum sodium concentrations at day 7	Primary	Serum sodium
Average area under the concentration-time curve of change from baseline in serum sodium concentrations up to day 60	Secondary	Serum sodium
Percentage of patients with worsening hyponatremia (a reduction of ≥ 3 mEq/L in serum sodium concentrations) during the treatment period	Secondary	Serum sodium
Percentage of patients with normalized serum sodium concentration (>135 mEq/L) at day 60	Secondary	Serum sodium
Change from baseline in body weight at day 2 (prior to day 2 dosing)	Other	Aquaresis
Change from baseline in patient-assessed dyspnea at 8 hours and at 24 hours from first dose	Other	Aquaresis
Change from baseline in the recorded time to complete the Trail Making Test, Part B, at day 28	Secondary	Cognitive function
Change from baseline in the Medical Outcomes Study-6 cognitive function scale at day 28 and day 60	Other	Cognitive function
Days alive and out of the hospital (for cardiovascular causes) during the treatment period (up to 60 days from randomization)	Secondary	Morbidity and mortality
Adverse events	Safety	Safety
Vital signs	Safety	Safety
Clinical laboratory tests	Safety	Safety
12-lead electrocardiograms	Safety	Safety

Table 2. Study endpoints.

Once efficacy has been demonstrated for the primary efficacy endpoint, the 5 secondary efficacy endpoints will be analyzed as a fixed-sequence of hierarchical tests comparing the 2 treatment groups in the intent-to-treat (ITT; all randomized and treated) population. A test will be presented only if all previous tests in the sequence have been rejected at the 2-sided 0.05 level of significance. This will preserve the overall Type I error at 0.05 for the entire sequence of tests. Quantitative variables in the fixed sequence will be analyzed by analysis of covariance similarly to the primary endpoint, while categorical variables will be analyzed by the Cochran–Mantel–Haenszel test, adjusting for country and baseline serum sodium concentration. Other endpoints will be analyzed using similar analyses without adjustment for multiple testing. Sensitivity analyses will be performed using similar models with the data collected at different time points in the ITT population or on the primary, secondary, or other endpoints using the modified ITT population (all randomized and treated with one scheduled on-therapy assessment of serum sodium concentration).

Safety analyses will include comparison of treatment groups for the incidence of treatment-emergent adverse events, serious adverse events, and adverse events related to study medication. Time point results and changes from baseline will be analyzed for clinical laboratory data, 12-lead electrocardiogram data, and vital signs.

Discussion

THE BALANCE study will evaluate the potential of lixivaptan to improve serum sodium concentrations in hospitalized patients with HF with fluid overload, pulmonary congestion, and hyponatremia. In addition, it will evaluate other possible clinical benefits of lixivaptan therapy. Based on the aforementioned association between reduced serum sodium concentrations and poor outcomes in hospitalized patients with HF and hyponatremia, it is reasonable to expect that correction of hyponatremia in this setting may improve overall outcomes. This hypothesis has not, however, been adequately tested in a clinical trial. Two other vasopressin antagonists have been evaluated in patients with HF: conivaptan and tolvaptan. Conivaptan, a mixed V_1/V_2 AVP receptor antagonist, is available in an intravenous formulation for acute use only. Tolvaptan, a selective, orally available V_2 receptor blocker, has been predominantly tested in normonatremic HF subjects. Clinical trials of these agents also varied with regard to design, dosing, treatment duration, and primary endpoints, and although short-term improvements in symptoms were noted, neither demonstrated any beneficial effect on mortality or HF-related morbidity.^{16,18,19,22,23}

THE BALANCE study will be, to our knowledge, the largest prospective study conducted to evaluate a vasopressin antagonist exclusively in patients with HF and hyponatremia. Patients will be stratified by baseline serum sodium concentration to further define the potential benefits of correcting mild hyponatremia relative to benefits associated with correction of moderate to severe hyponatremia. THE BALANCE study also is unique in that it will allow inclusion of patients with preserved left ventricular ejection fraction. Inclusion of these patients is important because clinical trial data regarding the efficacy of HF treatments are relatively scarce in this population,²⁴ and these patients comprise 50% of all hospitalizations for worsening HF.²⁵

THE BALANCE study seeks to determine the benefit of serum sodium correction both during acute treatment with lixivaptan and

during the on-treatment follow-up phase. The primary endpoint of THE BALANCE study is the change from baseline in serum sodium concentrations at day 7 of treatment. To achieve optimal improvements in serum sodium concentration with lixivaptan, THE BALANCE study design includes an initial dose titration period of 3 days after randomization (rather than a fixed dose regimen, as in some other studies) and allows for additional discretionary dose adjustments by the investigator throughout the study. The ability to administer lixivaptan either once or twice daily provides further flexibility in dosage titration. Longer-term benefits of lixivaptan will be assessed by evaluating the mean number of days alive and out of the hospital observed with lixivaptan versus placebo over the 60-day treatment period.

The presence and potential changes in cognitive function will also be assessed in THE BALANCE study utilizing the TMT-B test. The TMT-B is a rater-administered, performance-based measure of a subject's cognitive functioning including executive function, motor speed and visual attention. The test has high inter-rater reliability²⁶ and has been used to assess cognition in randomized, controlled clinical trials in a variety of conditions including schizophrenia,²⁷ Alzheimer's disease,²⁸ and following coronary artery bypass grafting or coronary angioplasty.²⁹ Neuropsychological studies have shown the TMT-B to be one of the most sensitive general indicators of brain damage and disease, regardless of etiology. Chronic hyponatremia (including mild hyponatremia) has been associated with cognitive impairment, gait disturbances, and falls in the general population.³⁰ Improvements in hyponatremia in heart failure patients may also translate into clinical benefits impacting daily functioning and reducing the potential for morbidities associated with decreased cognition, gait disturbances, and falls.³⁰ The change in the time to complete the TMT-B from baseline to day 28 will be used as the primary measure of improvements in cognitive function.

Conclusions

THE BALANCE study will evaluate the efficacy and safety of lixivaptan in patients with HF and hyponatremia requiring hospitalization. The main objectives of the study are to determine whether lixivaptan can correct hyponatremia, maintain normal serum sodium concentrations, and improve cognitive function and clinical outcomes in patients with HF.

Conflicts of Interest

Funding for this study was provided by Biogen Idec, Inc., and Cardiokine, Inc.

Dr. Abraham has received consulting fees from Biogen Idec and Cardiokine. Drs. Aranda, Elkayam, Gilbert, Kukin, Lowes, and Tavazzi have no conflicts to disclose. Drs. Boehmer and O'Connell have received consulting fees from Cardiokine. Dr. Gottlieb has received consulting fees and grant support from Biogen Idec and Cardiokine. Dr. Hasenfuß has received honoraria from and serves on an advisory board for Cardiokine. Dr. Feldman owns equity interests in Cardiokine. Dr. Ticho is an employee of and owns equity interest in Biogen Idec. Dr. Orlandi is an employee of and owns equity interest in Cardiokine.

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