

Tolvaptan, hyponatremia, and heart failure

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Abstract: Tolvaptan is the first FDA-approved oral V_2 receptor antagonist for the treatment of euvolemic and hypervolemic hyponatremia, in patients with conditions associated with free water excess such as heart failure, cirrhosis, and the syndrome of inappropriate antidiuretic hormone secretion. Tolvaptan inhibits the binding of arginine vasopressin to the V_2 receptors on the collecting ducts of the kidneys resulting in aquaresis, the electrolytes sparing excretion of water. This article reviews the accumulated experience with tolvaptan and all the major clinical trials that were conducted to study its safety and efficacy and concludes by summarizing clinicians' views of its current application in clinical practice.

Keywords: arginine vasopressin antagonist, tolvaptan, heart failure, hyponatremia

Introduction

Hyponatremia is the most common electrolyte abnormality seen in hospitalized patients¹ and is associated with increased morbidity that includes cognitive impairment,² falls,² fractures, and osteoporosis;^{3–5} longer hospital stay; and increased mortality.^{1,6–8} It is traditionally defined as serum $\text{Na}^+ \leq 135$ mEq/L.¹ However, serum Na^+ concentration ≤ 138 mEq/L was found to be associated with worsened outcome,^{6–9} so hyponatremia should be redefined as serum Na^+ concentration ≤ 138 mEq/L.¹⁰

Since Na^+ is the major determinant of plasma osmolality, hyponatremia is usually associated with hyposmolality. It may present as euvolemic hyponatremia as seen in the syndrome of inappropriate antidiuretic hormone secretion (SIADH), or hypervolemic hyponatremia in edema-forming conditions such as heart failure (HF) or cirrhosis. Hypovolemic hyponatremia is due to conditions promoting renal or extra-renal Na^+ loss.¹

The clinical manifestations of hyponatremia include malaise, headache, nausea, vomiting, lethargy, confusion, stupor, seizure, and coma, depending on the severity of hyponatremia and the rapidity of its development.¹ However, hyponatremic patients frequently have subtle symptoms, and are often perceived as asymptomatic, which explains why hyponatremia is frequently undiagnosed and untreated.¹¹

Given the limitations to the traditional treatment of hyponatremia, fluid restriction with or without the use of lithium, demeclocycline, and urea, the introduction of vasopressin antagonists with their ability to induce aquaresis, the electrolyte free excretion of water, has provided an attractive option to the treatment of hyponatremia by directly opposing the action of arginine vasopressin (AVP).

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Arginine vasopressin and its receptors

AVP is a peptide hormone composed of 9 amino acids that plays a major role in preserving water balance, osmolality, and blood volume. It is synthesized in the hypothalamus, stored in the posterior pituitary gland, and then released as needed into the hypophyseal portal vein.¹¹

Under normal conditions, the release of AVP is controlled primarily by osmolality. Osmoreceptors located in several areas of the brain are very sensitive to changes in serum osmolality. A rise in serum osmolality by 1% will stimulate the release of AVP, and in sequence increase water re-absorption at the renal tubule, causing water retention.^{12,13}

Change in the circulating blood volume is the second mechanism by which AVP is stimulated. The baro-receptors in the carotid sinus and stretch receptors in the wall of the great veins, atria, and pulmonary trunk are sensitive to changes in the volume status (eg, volume depletion and/or hypotension).^{14,15} As low as 5% to 10% decrease in blood volume will lead to AVP release and subsequent water retention to restore the intravascular volume.^{14,15} This occurs in conditions characterized by arterial under-filling, such as HF due to low cardiac output and liver cirrhosis due to vasodilatation.

The release of AVP is accounted for predominantly by the above 2 mechanisms, but its secretion is also affected by other factors including endogenous angiotensin II, stress, and pain.^{15,16}

AVP receptors are G protein-coupled receptors that mediate cardiovascular and renal functions. There are 3 subtypes (V_{1A} , V_{2} , and V_{1B}). Table 1 summarizes the location and functions of the different receptors.^{17–20}

Arginine vasopressin antagonists

The first non-peptide AVP antagonist was discovered in 1992 and subsequently several had been developed.²¹ By binding to the V_2 receptors, they prevent the cascade leading to the insertion of aquaporin 2 (AQP-2) water channels

into the luminal membrane of the principal cells and water reabsorption.¹⁹ Conivaptan is the first intravenous dual V_{1A}/V_2 receptor antagonist approved by the US Food and Drug Administration (FDA) and tolvaptan is the first oral antagonist.

Tolvaptan

Tolvaptan (OPC-41061) is a potent, orally active, non-peptide V_2 receptor antagonist. It was the first oral AVP receptor antagonist to be approved (in May 2009) by the FDA for the treatment of hypervolemic or euvolemic hyponatremia (associated with HF, cirrhosis, or SIADH) with either a serum Na^+ concentration <125 mEq/L or less marked hyponatremia that is symptomatic and resistant to fluid restriction.²⁰ It is produced by Otsuka Pharmaceutical Co Ltd, Rockville, MD and is available under the brand name Samsca®.²²

Pharmacokinetics and pharmacodynamics

Tolvaptan is a selective V_2 receptor antagonist with an affinity for the V_2 receptor that is 1.8 times that of native AVP. Tolvaptan's affinity for the V_2 receptor is 29 times greater than its affinity for the V_{1A} receptor.²³

The pharmacokinetics of tolvaptan have been studied in healthy subjects at different single or multiple daily doses of up to 480 mg. For single oral doses ranging from 60 to 480 mg, the area under the curve (AUC) increases proportionally with dose. The apparent clearance was independent of the dose at clinically used doses.²⁴

The time to peak concentration (T_{max}) was observed ≈ 2 to 4 hours post-dose. The absolute bioavailability of tolvaptan is unknown, but at least 40% of the dose is absorbed as tolvaptan or metabolites, and its absorption is not affected by food intake. Tolvaptan is highly bound to plasma protein (99%), and its volume of distribution is about 3 L/kg in healthy subjects, and slightly higher in patients with HF.²⁵ The estimated $t_{1/2}$ of tolvaptan is slightly shorter than 12 hours.²⁰

From 0 to 12 hours post-dose, mean urine volume, free water clearance, and urine osmolality were similar for

Table 1 Arginine vasopressin receptors^{18–21}

Receptor	Location	Function
V_{1A}	Vascular smooth muscle cells, hepatocytes, platelets, uterus, renal, adrenal, and brain cells.	Vasoconstriction, glycogenolysis, platelet aggregation, and myocytes hypertrophy.
V_{1B}	Anterior pituitary gland	Mediate the release of adrenocorticotropin hormone and endorphines.
V_2	Collecting ducts of the kidney.	Mediate free water absorption by mobilizing intracellular vesicles of aquaporin-2 (AQP2) to the apical plasma membrane of the collecting duct cells, causing an increase in water permeability and antidiuretic effect.

all doses, but 12 to 24 hours post dose, the mean free water clearance generally increased with increasing dose, and urine osmolality decreased with increasing dose.²⁴ Throughout the 0- to 24-hour period, increases were seen in mean serum Na⁺ concentration (~4–6 mEq/L), plasma osmolality (~8 mOsm/kg), and free water clearance (~6 mL/min); while mean urine concentration of Na⁺ and potassium (K⁺) were decreased to less than 20 mEq/L with no change in the serum K⁺ concentration.²⁴ Co-administration of tolvaptan and furosemide produced a higher increase in urine volume and free water clearance, a greater decrease in urinary osmolality, and no further increase in rennin activity and aldosterone concentration, compared with furosemide alone.²⁶

Drug formulation and dosing

Tolvaptan is present in tablet form with different shapes according to the dosage. It is available in 15, 30, and 60 mg strengths. It should be stored at controlled room temperature between 59° and 86°F (15–30°C) and can be administered with or without food.²² The recommended starting dose is 15 mg/day, which may be increased at intervals ≥24 hour to 30 mg/day, and to a maximum of 60 mg/day.

Close monitoring of the serum Na⁺ and volume status is a necessity to avoid complication from rapid correction of hyponatremia (eg, osmotic demyelination). Fluid restriction should be avoided during the first 24 hours of therapy, and patients should be advised to continue fluid ingestion in response to thirst.

Metabolism and drug interaction

Tolvaptan is metabolized mainly in the liver, primarily by cytochrome P450 (CYP 3A), and <1% is excreted unchanged in the urine.²⁴ The co-administration of tolvaptan with ketoconazole or other strong CYP 3A inhibitor (eg, clarithromycin, itraconazole, telithromycin, saquinavir, nelfinavir, ritonavir, and nefazodone) decreases the total clearance of tolvaptan and increases tolvaptan concentrations. The co-administration of grapefruit juice and tolvaptan results in a 1.8-fold increase in tolvaptan exposure.²⁷ On the other hand, the co-administrations of tolvaptan with rifampin or other CYP 3A inducers (eg, rifabutin, rifapentin, barbiturates, phenytoin, carbamazepine, and St John's Wort) results in increased metabolism of tolvaptan, which decreases its effects.^{20,28}

Tolvaptan shows no significant pharmacokinetic interactions with amiodarone, warfarin, furosemide, or hydrochlorothiazide.^{29,30} Also, there was no clinically relevant change in lovastatin or digoxin effects when co-administered with tolvaptan.^{28,31}

Contraindications, precautions, and side effects

Tolvaptan is contraindicated with the use of a strong CYP 3A inhibitor due to drug interaction. It is also contraindicated in hypovolemic hyponatremia because it might precipitate hypotension and renal failure. It should not be administered in anuric patients due to expected lack of clinical benefit. Patients who are unable to sense or appropriately respond to thirst stimulation should not take tolvaptan because this increases the risk of rapid correction of serum Na⁺.

Tolvaptan use in pregnancy is category C, so it should be used only if the potential benefit justifies the potential fetal risk, and it is excreted into the milk of lactating rats, so that mothers should discontinue nursing or stop tolvaptan.

The FDA has restricted the initiation and re-initiation of tolvaptan to the hospital setting, where the serum Na⁺ can be monitored closely. Since rapid correction of hyponatremia (>12 mEq/L/day) may cause osmotic demyelination resulting in severe neurological complications and possible death, caution should be advised with concomitant use of tolvaptan and hypertonic saline.

The most common adverse reactions (incidence ≥5%) when tolvaptan was administered at a dose ranging from 15 to 60 mg/day, were thirst, dry mouth, asthenia, constipation, polyuria, and hyperglycemia.²²

Constipation, diarrhea, esophageal varices, thirst, malaise, pyrexia, increased blood uric acid and glucose, anorexia, insomnia, pollakiuria, nausea, vomiting, cough, hypo- and hyperkalemia, hypotension, dizziness, chest pain, anemia, headache, urinary tract infection, renal failure, pneumonia, ventricular tachycardia, atrial fibrillation, pain in extremity, and dry skin and mouth were side effects reported in clinical trials.^{32,33}

Tolvaptan in the treatment of hyponatremia

Given the aquaretic effect of tolvaptan, initial clinical trials assessed its role in the management of hyponatremia. In order to compare tolvaptan to fluid restriction for the management of euvoletic and hypervolemic hyponatremia, a multicenter, prospective, randomized, open-label, active-controlled, dose titration trial was conducted.³⁴ Hyponatremic patients with serum Na⁺ concentration <135 mEq/L for 2 or more consecutive days were eligible (Table 2).

The primary outcome was normalization of serum Na⁺ concentration (≥135 mEq/L or ≥10% increase in serum Na⁺ level from baseline to the last inpatient assessment).

Table 2 Tolvaptan studies in hyponatremic patients

Reference Design	Intervention	Patient population	Major measures	Major results
Multicenter, prospective, randomized, open-label, active-controlled, dose titration ³⁴	Patients were randomized to tolvaptan or fluid restriction with placebo	n = 28 Hyponatremic patients with serum Na ⁺ concentration <135 mEq/L	Normalization of serum Na ⁺ concentration	A total of 11 patients normalized their Na ⁺ levels by the last inpatient visit in the tolvaptan group compared to 3 patients in the placebo group (<i>P</i> = 0.049) 50% of the patients achieved normalization in their Na ⁺ level within 4 days in the tolvaptan group compared to 8 days in the fluid restriction group (<i>P</i> < 0.03) Tolvaptan patients had significantly larger increases in mean serum Na ⁺ from baseline
Two randomized, double-blind, placebo-controlled, Phase III trials ³⁵	Patients were randomized to receive 15 mg/day of oral tolvaptan or placebo for 30 days	n = 448 Euvolemic or hypervolemic hyponatremic patients	The change in the average daily area under the curve (AUC) for the serum Na ⁺ concentration from baseline to day 4 and day 30 The percentage of patients with normalized serum Na ⁺ concentration at day 4 and 30	Tolvaptan significantly increased the average daily AUC for the serum Na ⁺ concentration from baseline to study day 4 and during the entire 30-day study period as compared with placebo Significantly more patients in the tolvaptan group had normal serum Na ⁺ concentration and fewer patients had marked hyponatremia at day 4 and day 30, as compared with placebo
Open-label extension of the SALT-1 and SALT-2 trials ³⁶	4-year sequential, open-label extension of the SALT-1 and SALT-2 trials	n = 111 Euvolemic or hypervolemic hyponatremic patients	Evaluate the safety and efficacy of long-term tolvaptan use in hyponatremia	Multiple adverse events were judged to be related to tolvaptan
Post hoc analysis on the SALT trials ³⁷	7 patients were randomized to receive tolvaptan and 12 to placebo	n = 19 Schizophrenic patients with idiopathic hyponatremia	Evaluate the effects of tolvaptan on idiopathic hyponatremia in schizophrenia	Tolvaptan patients had significantly greater increase in the average daily AUC for Na ⁺ concentration from baseline to day 4, as compared with placebo Mean serum Na ⁺ concentrations were significantly higher at all measurement times after receiving the study medication except at 8 hours, where it was marginally different (<i>P</i> = 0.07)

After 2-day placebo run-in period, patients were randomized to tolvaptan or fluid restriction with placebo in a 2:1 ratio for the duration of their inpatient stay or 12 days, whichever occurred first. Tolvaptan was started at 10 mg/day with daily incremental increases to 15, 30, 45, and 60 mg/day as needed to achieve a normal serum Na⁺ level. Fluid restriction was started at 1200 mL/day in the placebo group, and adjusted by the investigator to achieve normal serum Na⁺ levels. The study treatment was continued during the outpatient maintenance period if serum Na⁺ level normalized before day 14, otherwise subjects could be withdrawn to allow physicians to administer other treatments. The tolvaptan dose or the placebo dose with fluid restriction was maintained at the same level throughout the maintenance period (days 15–28).

A total of 28 patients were enrolled in the study; 17 were randomized to tolvaptan, and 11 to placebo with fluid restriction. Patients were 66 ± 13 and 67 ± 9 years

of age (mean ± SD) in the tolvaptan and placebo groups, respectively. Women were 41% and 45% in the tolvaptan and placebo groups, respectively. HF was the cause of hyponatremia in 50%, 14% had cirrhosis, and 36% had SIADH or other cause. The mean (± SD) baseline serum Na⁺ levels were 129 ± 3 mEq/L (tolvaptan), and 129 ± 4 mEq/L (placebo). In the tolvaptan group, 2 out of the 17 patients were withdrawn during the run-in period because of protocol violations or meeting withdrawal criteria. The remaining 15 patients received tolvaptan, but only 12 completed the treatment period and received the study drug during the maintenance period, the rest had adverse events preventing them from completing the study. Only 6 patients completed the 28-day outpatient maintenance period, the other 6 patients were withdrawn due to adverse events (1 patient), losing follow up (1 patient), meeting withdrawal criteria (2 patients), and withdrawing consent due to personal reasons (2 patients). In the placebo group, 3 out of the 11 patients were withdrawn

during the run-in period because of protocol violations or meeting withdrawal criteria. The remaining 8 patients received placebo and were placed on fluid restriction; however only 2 patients completed the treatment period and both of them completed the 28-day outpatient maintenance period. The other 6 patients were withdrawn due to adverse events (2 patients), insufficient response (1 patient), meeting withdrawal criteria (1 patient), and withdrawing consent due to lack of effect (2 patients).

The mean \pm SD dose of tolvaptan was 26 ± 15 and 28 ± 18 mg/day during the initiation phase and maintenance phase, respectively. The mean \pm SD duration of treatment with tolvaptan was 7 ± 3.6 and 14 ± 8 days in the initiation phase and maintenance phase, respectively. Tolvaptan patients had significantly larger increases in mean serum Na^+ from baseline, which was observed as early as 4 hours after the first dose, reached plateau by day 5, and persisted through the last inpatient visit, compared with fluid restriction patients. The mean \pm SD change in serum Na^+ level was 4.7 ± 3.1 and -0.3 ± 4 in the tolvaptan and placebo groups, respectively ($P = 0.039$). A total of 11 patients normalized their Na^+ levels by the last inpatient visit in the tolvaptan group compared with 3 patients in the placebo group ($P = 0.049$). Half the patients (50%) achieved normalization in their Na^+ level within 4 days in the tolvaptan group compared with 8 days in the fluid restriction group ($P < 0.03$).

As expected, urine output was significantly higher in the tolvaptan group at baseline and at the last inpatient day compared with fluid restriction group. No differences in serum K^+ , blood pressure, heart rate, thirst score, or adverse effects requiring drug discontinuation were observed between the 2 groups.

This study showed that tolvaptan without fluid restriction was more effective than fluid restriction alone in normalizing hyponatremia. However it is limited by small sample size, the number of subjects who withdrew early, and the short-term follow up.

The SALT-1 and SALT-2 trials (Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2) are 2 relatively large, randomized, double-blind, placebo-controlled, phase III trials conducted to evaluate the effect of tolvaptan on euvoletic and hypervolemic hyponatremic patients (Table 2).³⁵

Patients with euvoletic or hypervolemic hyponatremia (serum Na^+ concentration <135 mEq/L) were included. Exclusion criteria included psychogenic polydipsia, head trauma, postoperative conditions, uncontrolled hypothyroidism or adrenal insufficiency, any hyponatremic condition associated with the use of medications that can be safely stopped, or hypovolemic hyponatremia.

The patients were randomized to receive 15 mg/day of oral tolvaptan in the morning or matching placebo for 30 days. Fluid restriction was not mandatory, but treatment with lithium, demeclocycline, or urea was not permitted. The tolvaptan dose was adjusted to maintain a serum Na^+ concentration between 135 and 145 mEq/L, per study protocol. Patients were hospitalized the first day of the study and the majority were discharged by day 4.

Patients' evaluation was conducted at baseline, 8 hours after drug administration, and in days 2, 3, 4, 11, 18, 25, 30, and 37. The study medication was stopped at 30 days, and the effect of discontinuation was studied on the last evaluation (day 37). The 2 primary end points of the study were: the change in the average daily AUC for the serum Na^+ concentration from baseline to day 4 and day 30. Secondary outcomes included the change in the AUC for serum Na^+ concentration in patients with marked hyponatremia, the absolute serum Na^+ concentration at each visit, the time to normalization of serum Na^+ concentration, the percentage of patients with normalized serum Na^+ concentration at day 4 and 30, the categorical serum Na^+ concentration at day 4 and 30 (normal, >135 mEq/L; mild hyponatremia, 130–135 mEq/L; or marked hyponatremia, <130 mEq/L), fluid intake and output at day 1, change in body weight in hypervolemic patients at day 1, fluid restriction or use of rescue intravenous saline, and the change in scores on the physical component summary and mental component summary of the medical outcomes study 12-item short-form (SF-12) general health survey.

In the SALT-1 trial, 205 patients were randomized; 102 patients received tolvaptan, and 103 patients received placebo. The percentage of patients who completed the trial (30-day study period and 7-day follow up) was 77.5% in the tolvaptan group and 63.1% in the placebo group. Mean (\pm SD) age was 60 ± 14 and 60 ± 13 in the tolvaptan and placebo groups, respectively. Females were 49% and 40% in the tolvaptan and placebo groups, respectively. In the SALT-2 trial, 243 patients were randomized; 123 patients received tolvaptan, and 120 patients received placebo. The percentage of patients who completed the trial was 74.8% in the tolvaptan group and 74.2% in the placebo group. Mean (\pm SD) age was 62 ± 15 and 63 ± 14 in the tolvaptan and placebo groups, respectively. Females were 39% in both tolvaptan and placebo groups. The patients' demographic and baseline characteristics were similar in the study groups of both trials.

Tolvaptan significantly increased the average daily AUC for the serum Na^+ concentration from baseline to study day 4 and during the entire 30-day study period compared

with placebo. Tolvaptan significantly increased serum Na^+ concentration within 8 hours of administration compared with placebo, in both trials. This statistical superiority was maintained at all subsequent visits. With tolvaptan, the serum Na^+ concentration approached the normal range more rapidly, compared with placebo in both trials. At day-37, after discontinuation of the study medication, there was no statistical difference in serum Na^+ concentration in both SALT-1 and SALT-2 trials.

In both trials, significantly more patients in the tolvaptan group had normal serum Na^+ concentration and fewer patients had marked hyponatremia at day 4 and day 30, compared with placebo. On day-30, scores on the physical component summary of the SF-12 health survey did not differ significantly between the groups in both trials. However, the mental component summary improved in the tolvaptan group in the combined analysis of both trials ($P = 0.02$), in SALT-1 ($P = 0.04$), and in the combined subgroup of marked hyponatremia ($P = 0.04$), but not in SALT-2 ($P = 0.14$).

In both trials, the following side effects were observed in the tolvaptan group: dehydration with hypotension, dehydration with dizziness, syncope, acute renal failure, ascites, increased serum Na^+ and creatinine concentrations, and *E. coli* sepsis with respiratory failure. In the tolvaptan group, eight patients were withdrawn from the study due to adverse events that were potentially related to the study treatment; rash, dysgeusia, nocturia, urinary frequency, exanthema, muscle weakness, and hypernatremia. The number of deaths in the 2 groups within the defined observation period was similar. In the tolvaptan group, only 4 patients exceeded the desirable rate of Na^+ correction during the first 24 hours (>0.5 mEq/L/hour), and the maximum observed rate was 0.61 mEq/L/hour. In the tolvaptan group, 1.8% of the patients had a serum Na^+ concentration >146 mEq/L.³²

The 2 trials unequivocally proved that tolvaptan, when added to standard therapy, was superior to placebo in raising and maintaining serum Na^+ concentration in patients with euvoletic and hypervolemic hyponatremia of diverse etiologies. They also showed that the benefit was confined to its continuous usage without long lasting effect.

The SALTWATER trial (Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real world conditions) was a 4-year sequential, open-label extension of the SALT-1 and SALT-2 trials (Table 2).³⁶ It was conducted to evaluate the safety and efficacy of long-term tolvaptan use in hyponatremia. Out of the 325 patients who completed the SALT-1 and SALT-2 trials, 111 were

enrolled (38 patients from SALT-1, and 73 from SALT-2). In this study, 49.5% of the patients were men, and the mean (\pm SD) age of patients was 64.6 ± 15.0 . The median time from completion of SALT-1 and SALT-2 trials to enrollment in the SALTWATER was 30 days per patients. A total of 64 of the enrolled patients discontinued treatment during the follow up period for a variety of reasons. Mild hyponatremia was seen in 46.8% of the patients (serum Na^+ concentration between 130–134 mEq/L), and the rest had marked hyponatremia (serum Na^+ concentration < 130 mEq/L) at baseline in SALT-1 and SALT-2. Upon enrollment in SALTWATER, 15.3% of the patients had normal serum Na^+ concentration, 53.2% had mild hyponatremia, and 31.5% had marked hyponatremia. HF was the etiology of hyponatremia in 29.7% of the patients, while cirrhosis accounted for 18.0%, and SIADH and other causes were 52.3%. The mean dose of tolvaptan was increased to 30 mg/day during the first 16 to 20 weeks, and maintained at that level for the rest of the study period.

The patients were followed while they were on tolvaptan therapy for a mean of 701 days. During that time, 105 patients had adverse effects. Pollakiuria, thirst, fatigue, dry mouth, polydipsia, polyuria, hypotension, hypernatremia, dizziness, headache, peripheral edema, and acute renal failure were the most common adverse effects that were judged to be tolvaptan-related.

A total of 64 patients were withdrawn from the study. Adverse effects were the reason for withdrawal in 19 patients from which 6 patients died (cardiac failure, esophageal varices, hepatic cirrhosis, cerebral hemorrhage, and gastrointestinal hemorrhage). The adverse effects in the surviving 13 patients were ventricular tachycardia, vertigo, gastrointestinal hemorrhage, vomiting, gait disturbance, irritability, increase in serum creatinine or Na^+ , anorexia, bladder cancer, dysphasia, myocardial infarction, psychotic disorder, renal failure, and pruritus. Out of those, severe ventricular tachycardia, severe irritability, mild increase in serum Na^+ , mild anorexia, severe increase in serum creatinine, and moderate pruritus were judged to be possibly or probably related to tolvaptan.

An additional 13 patients died as an outcome of an adverse effect without being withdrawn from the study (cardiac failure, renal failure, respiratory failure, cardiac arrest, cardiorespiratory arrest, hepatorenal syndrome, pneumonia, cerebral hemorrhage, sepsis, and urosepsis), giving a total of 19 deaths. Out of the 19 patients who died, only the death of the patient with the severe hepatorenal syndrome was judged to be possibly related to tolvaptan. Five patients

had >1 mEq/L/hour increase in serum Na^+ concentration within the first 8 hours, and 18 patients had serum Na^+ concentration >145 mEq/L at individual time points (1 was withdrawn from the study, while the hyponatremia resolved in the other 17 patients).

Serum Na^+ concentration at baseline ranged between 114 and 141 mEq/L with a mean (\pm SD) of 130.8 ± 4.4 mEq/L. Correction of serum Na^+ levels occurred at similar rates during the first 8 hours in SALTWATER and the SALT-1 and SALT-2, and by day 14, serum Na^+ levels reached similar plateau. After the initial titration period, mean serum Na^+ levels remained normal throughout the study period (>4 years). The rate of serum Na^+ correction was greater at the beginning in the subgroup of patients with marked hyponatremia, but similar kinetics were observed in the mild and marked hyponatremia groups, and in the HF and SIADH/other cause groups. Patients with cirrhosis had a trend of lower final serum Na^+ levels. More than 60% of the marked hyponatremia group and 45% of the mild hyponatremia group had normal Na^+ level by week 4. Similar serum Na^+ level correction rates were observed in the HF and SIADH/other cause groups, whereas cirrhosis patients had lower rates.

Serum Na^+ levels declined in all patient subgroups by day 7 of withholding tolvaptan. The percentage of the patients who had ≥ 3 mEq/L drop in their Na^+ level with tolvaptan discontinuation was 68%, and a similar proportion of patients dropped to <135 mEq/L. In the mild and marked hyponatremia subgroups, 122.3 ± 184.3 and 162.5 ± 186 days were the mean (\pm SD) time for first fluid restriction, respectively. Fluid restriction was required in 13.2% and 5.4% of patients in the mild and marked hyponatremia subgroups, respectively.³³ The study proved that the effect of tolvaptan on increasing serum Na^+ concentration was maintained long term, and although there were numerous adverse events the trial did not have a comparator group of an equally ill cohort treated with placebo over this long period of time.

Josiassen et al conducted a post hoc analysis on the SALT trials to evaluate the effects of tolvaptan on idiopathic hyponatremia in schizophrenia (Table 2).³⁷ A total of 24 subjects in the SALT trials had schizophrenia or schizoaffective disorder, and 19 of them had idiopathic hyponatremia. The other 5 patients had HF (2 patients) or liver cirrhosis (3 patients) as a cause for their hyponatremia; hence they were excluded from this analysis. Out of the 19 subjects, 7 were randomized to receive tolvaptan and 12 to placebo. Mean age (\pm SD) was 52.3 ± 10.4 and 49.6 ± 10 years in the tolvaptan and placebo groups, respectively. Males were 57.1% and 91.7% in the tolvaptan and placebo groups, respectively. The

baseline characteristics of the 2 groups were similar except for the dose of antipsychotic medications which was higher in the tolvaptan group.

Tolvaptan patients had significantly greater increase in the average daily AUC for Na^+ concentration from baseline to day 4, compared with placebo (mean \pm SD were 5.14 ± 3.14 vs 0.91 ± 2.6 mEq/L, respectively, $P = 0.0055$). The same was also observed from baseline to day 30; 7.51 ± 2.75 mEq/L (mean \pm SD) in the tolvaptan group compared with 1.39 ± 1.9 mEq/L (mean \pm SD) in the placebo group ($P < 0.001$). Mean serum Na^+ concentrations were significantly higher at all measurement times after receiving the study medication except at 8 hours, where it was marginally different ($P = 0.07$). Subjects on higher doses of antipsychotic drugs showed greater improvement in their serum Na^+ concentration. Only 1 subject (on placebo) required fluid restriction, and no subject required rescue therapy or had excessive increase in serum Na^+ concentration.

No significant changes in serum creatinine or K^+ concentrations were noticed. In the tolvaptan group, 2 patients experienced dehydration and hypotension; 1 was judged to be unrelated to tolvaptan, and the other was transient and due to patient misunderstanding of fluid restriction. No long-term adverse effects were observed, and moreover, no adverse symptoms were noticed after drug discontinuation.

This study showed the feasibility of using tolvaptan as a treatment of hyponatremia in this special population. However, this is a post hoc analysis of the SALT trials, and it would be desirable to target this population in future prospective trials.

Use of tolvaptan in heart failure

The SALT trials were 2 of the major trials conducted to evaluate the effects of tolvaptan in hyponatremic patients.³⁵ In both trials, HF was a major etiology for hyponatremia, accounting for 33% in the SALT-1, and 29% in the SALT-2.³⁵

Several randomized, double-blind studies were conducted in patients with HF to assess the effect of tolvaptan on congestion, hemodynamics, left ventricular remodeling, HF hospitalization, and survival.

A multicenter, randomized, double-blind, placebo-controlled trial was conducted to evaluate the effects of chronic tolvaptan use on congestion in patient with HF irrespective of their ejection fraction. Patients had to have HF symptoms for at least 30 days, and signs of volume overload at screening despite diuretic use for at least 30 days, with a fixed dose (40–240 mg) of furosemide for at least 7 days before enrollment. All patients received standard HF treatment.³⁸

The primary outcome of the study was the change in body weight on day 14 from baseline. Secondary outcomes included ankle edema, urine Na⁺ excretion, urine volume, and urine osmolality. Patients had 3-day run-in period (random assignment period) during which they were stratified for baseline furosemide dose (40–79 mg or 80–240 mg) and a separate random assignment was done in each stratum to maintain an overall balance between the different tolvaptan groups. After that period, they entered a 25-day treatment period in an outpatient setting. A total of 254 patients were enrolled in the study; 64, 64, 63, and 63 patients were randomized to 30, 45, or 60 mg tolvaptan, or placebo, respectively. Mean (\pm SD) ages were 67.6 ± 10.9 , 65.6 ± 13.1 , 68.5 ± 13.6 , and 65.1 ± 12.9 in the 30, 45, and 60 mg tolvaptan, and placebo, respectively. Men were 62.5, 60.9, 60.3, and 73.0% in the 30, 45, and 60 mg tolvaptan, and placebo, respectively. The percentage of patients completing the study was 87%.

The patients were to return to the clinic on day 3, 4, 7, 10, 14, 21, and 28 during the treatment period. A dose-dependent, statistically significant, decrease in body weight from baseline was observed on the first day of tolvaptan treatment at all doses and maintained throughout the study, as compared with placebo. The decrease in body weight was similar in all tolvaptan patients irrespective of left ventricular ejection fraction. Urine volumes were 3909, 4232, 4597, and 2328 mL in the 30, 45, and 60 mg tolvaptan, and placebo, respectively ($P < 0.05$, compared with placebo). Despite the increase in fluid intake with tolvaptan therapy, the mean net fluid losses were significantly higher as compared with placebo; 1337, 988, 1286, and 98 mL in the 30, 45, and 60 mg tolvaptan, and placebo, respectively ($P < 0.05$ at each dose). Urine osmolality decreased to a mean \pm SD of 15.47 ± 189.95 , 52.34 ± 164.69 , and 118.77 ± 131.66 mOsm/kg in the 30, 45, and 60 mg tolvaptan groups, respectively, while an increase of 135.81 ± 189 mOsm/kg was observed with placebo ($P < 0.05$). Tolvaptan was also associated with significantly higher total urinary Na⁺ excretion and lower urine Na⁺ concentrations compared with placebo ($P < 0.05$ for both).

Small mean increases (<4 mEq/L) in serum Na⁺ concentrations were observed with tolvaptan compared with small mean decreases (<1 mEq/L) with placebo. Serum Na⁺ concentrations remained within the normal limits in most of the tolvaptan-treated patients. Above normal increases in serum Na⁺ concentration were seen in 6, 11, 13, and 5% of the patients on 30, 45, and 60 mg tolvaptan, and placebo, respectively, but did not require correction. The observed changes in serum Na⁺ concentrations were significantly

different between tolvaptan groups and placebo group at all times except for the 45 mg group at day 25. Hyponatremia was seen in 28% of the patients in this study (serum Na⁺ concentration <136 mEq/L), and those patients showed greater increases in serum Na⁺ that remained within the normal range during the study (normalization was seen on day 1 in 80% of tolvaptan group vs 40% in placebo group, $P < 0.05$). However, normonatremic patients had an acute and transient increase in Na⁺ levels, with values returning to baseline within 3 weeks of therapy. Normalization of serum Na⁺ concentrations was maintained in 82% of tolvaptan group vs 40% of placebo group at the last treatment day ($P < 0.05$).

Statistically significant improvement in ankle edema was observed at all times with 45 mg of tolvaptan compared with placebo ($P < 0.05$). No significant differences in the quality of life, heart rate, diastolic blood pressure, systolic blood pressure, serum K⁺ concentrations, or renal function were observed between the placebo and tolvaptan groups. Dry mouth, thirst, polyuria, and urinary frequency were higher with tolvaptan.

This study suggests that tolvaptan decreases body weight, normalizes serum Na⁺ concentration in patients with hyponatremia, and ameliorates edema in patients with chronic HF with mild signs of congestion on chronic diuretic therapy. However, this study was limited to patients with mild signs of congestion, and the results do not necessarily apply to all patients with HF.³⁸

The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, phase 2 feasibility trial that was conducted to evaluate the short-term and intermediate-term effects of tolvaptan in patients hospitalized with HF.^{39,40} Patients were included in the study if they were admitted for worsening HF, had left ventricular ejection fraction $< 40\%$ within 1 year of admission, and systemic congestion (jugular venous distention, rales, or peripheral edema) after initial in-hospital therapy for HF.

Patients were screened within 72 hours and randomized within 96 hours of admission if they continued to have signs and symptoms of congestion despite standard therapy (including diuretics) and were randomized in a 1:1:1:1 ratio to tolvaptan 30, 60, or 90 mg/day or placebo. The study had an inpatient period (up to 10 days), and an outpatient period (7 weeks). Study drug was given daily at 9 am during the inpatient and outpatient periods. Patients were withdrawn from the study if they were hospitalized for >10 days after

first dose. During the outpatient period, patients were seen in the office on weeks 1, 3, 5, and 7, and a safety phone call was conducted 30 days after last dose administration.

The study had 2 primary end points: change in body weight at 24 hours, and worsening HF at 60 days (hospitalization for HF, unscheduled emergency department or office visit for HF requiring increased or new therapy, or death). Secondary end points included changes in dyspnea, jugular venous distention, rales, edema, body weight, urine output, serum electrolyte levels, length of hospital stay after randomization, diuretics use, and patient- and physician-assessed symptoms scale.

A total of 319 patients were randomized; 78 patients were assigned to 30 mg tolvaptan, 84 patients to 60 mg tolvaptan, 77 patients to 90 mg tolvaptan, and 80 patients to placebo. Mean (\pm SD) age was 62 ± 14 , 62 ± 13 , 62 ± 14 , and 60 ± 14 years in the 30, 60, and 90 mg tolvaptan and placebo groups, respectively. Men were 68%, 59.5%, 79.2%, and 75.0% in the 30, 60, and 90 mg tolvaptan and placebo groups, respectively ($P = 0.04$). There were no other differences between the groups except for history of percutaneous coronary intervention/coronary artery bypass graft ($P = 0.02$).

On the first day of treatment, dose-independent and significantly higher decreases in body weight were observed with tolvaptan treatment. The median (interquartile range) reductions were -1.80 (-3.85 to -0.50), -2.10 (-3.10 to -0.85), -2.05 (-2.80 to -0.60), and -0.60 (-1.60 to 0.00) kg for tolvaptan 30, 60, and 90 mg, and placebo groups, respectively; $P = 0.02$, 0.02 , and 0.009 for the three tolvaptan groups compared with placebo. The median (interquartile range) reductions in body weight from baseline to discharge were -3.30 (-7.30 to -1.35), -2.80 (-5.90 to -1.80), -3.20 (-5.80 to -1.60), and -1.90 (-4.20 to -0.50) kg for tolvaptan 30, 60, and 90 mg, and placebo groups, respectively; $P = 0.006$, 0.02 , and 0.06 for the 3 tolvaptan groups compared with placebo.

The mean \pm SD of the first day urine output was significantly higher in all tolvaptan groups compared with placebo; 4056.2 ± 2310.2 , 4175.2 ± 2695.4 , 4127.3 ± 2050.8 , and 2296.5 ± 1134.1 mL for the tolvaptan 30, 60, and 90 mg, and placebo, respectively ($P = 0.02$, <0.001 , and <0.001 for the three tolvaptan groups as compared with placebo). This difference was maintained throughout the hospitalization period. Fewer tolvaptan patients had dyspnea, jugular venous distention, and peripheral edema on discharge as compared with placebo, but the difference was statistically significant only with dyspnea ($P = 0.04$). No significant improvement in

the assessment scales were observed between the tolvaptan and placebo groups, and the median time between randomization and discharge was the same (4 days). There was no significant difference in worsening HF between the 2 groups during the outpatient period of the study. Diuretic use decreased in both groups after discharge, but the difference in the reduction was not statistically significant.

One day after randomization, serum Na^+ level increased by a mean \pm SD of 2.77 ± 3.56 , 3.38 ± 4.84 , and 3.5 ± 3.63 mEq/L in the tolvaptan 30, 60, and 90 mg groups, compared with a decrease in sodium concentration with placebo (-0.20 ± 3.12 mEq/L). Hyponatremia was seen in 21.3% of the patients (serum Na^+ concentration <136 mEq/L) at randomization, and they showed rapid increase and often normalization in their Na^+ levels that was maintained throughout the study. In post hoc analysis, total mortality was lower in the combined tolvaptan groups (10%) compared with placebo (22.5%) in patients with elevated blood urea nitrogen (BUN) (>29 mg/dL), but this did not reach a statistical significance ($P = 0.07$). Furthermore, total mortality was lower in the combined tolvaptan groups (5.6%) compared with placebo (17.8%) in patients with severe systemic congestion (presence of dyspnea, jugular venous distentions [JVD], and edema), and this was statistically significant ($P = 0.03$). However, post hoc analysis results can only be used as hypothesis generating results to guide future prospective studies. Tolvaptan did not cause any hypotension, tachycardia, worsening renal function, or abnormalities in serum K^+ level, however, thirst was more frequently encountered.

This study indicated that tolvaptan, on top of standard HF therapy including diuretics, increased net fluid loss resulting in lower body weight compared with standard therapy alone in patients hospitalized for HF. Tolvaptan also improved serum Na^+ levels in patients with hyponatremia.

In order to evaluate the effect of tolvaptan on short term symptoms and long term outcome of patients with HF³⁶ the Efficacy of Vasopressin antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) was conducted.⁴¹

EVEREST consisted of three studies; 2 identical studies designed to investigate the short-term effects of tolvaptan on the clinical status and symptoms and an outcome study consisting of all randomized patients, designed to investigate long-term clinical outcome. The outcome study had 2 primary end points: all cause mortality and the composite of cardiovascular death and rehospitalization for HF. The secondary outcomes included the composite of cardiovascular mortality or cardiovascular rehospitalization, incidence of cardiovascular mortality, incidence of clinical

worsening of HF (death, hospitalization for HF, or unscheduled visit for HF), changes in body weight at day 1, serum Na^+ level at day 7 or discharge in patient with a baseline serum Na^+ level <134 mEq/L, edema score at day 7 or discharge in those with a baseline edema, patient-assessed dyspnea in those with dyspnea at baseline, and Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score at outpatient week 1. Tertiary end points included change in KCCQ domains at outpatient weeks 1 and 24, and at end of treatment.

EVEREST was a prospective, international, multicenter, randomized, double-blind, placebo-controlled study.^{32,41} Patients hospitalized for HF exacerbation were eligible to participate in the study within 48 hours of admission. The patients had to have reduced left ventricular ejection fraction ($\leq 40\%$), and signs of volume expansion. Patients with supine systolic blood pressure < 90 mmHg, serum creatinine level > 3.5 mg/dL, serum K^+ level > 5.5 mEq/L, and hemoglobin level < 9 g/dL were excluded.

Patients were randomly assigned to receive 30 mg/day of oral tolvaptan or placebo. The study included an inpatient treatment period and post-discharge treatment and follow up period. Patients received the study drug for a minimum of 60 days. All patients received standard HF therapy including diuretics, digoxin, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers, β -blockers, aldosterone blockers, hydralazine, and/or nitrates.

The study randomized 4133 patients; 2072 received tolvaptan and 2061 received placebo. The mean (\pm SD) age was 65.9 ± 11.7 and 65.6 ± 12.0 in the tolvaptan and placebo groups, respectively. Males were 73.4% and 75.4% of the patients in the tolvaptan and placebo arms, respectively. A total of 9 patients in the tolvaptan group and 6 patients in the placebo group did not receive the study medication, and hence were excluded from the safety analysis. During the study, 22% of the tolvaptan patients and 21% of the placebo patients discontinued the study medication prematurely within a median time of 8 months from randomization. Patients were followed for a median duration of 9.9 months.³²

The first primary end point (all cause mortality) was not different; 25.9% vs 26.3% in the tolvaptan vs placebo groups (Hazard Ratio 0.98; 95% CI 0.87–1.11; $P = 0.68$). The second primary end point (death from cardiovascular causes or first hospitalization for HF) was reached in 42.0% of the patients on tolvaptan compared with 40.2% in the placebo group (hazard ratio 1.04; 95% CI 0.95–1.14; $P = 0.55$). The composite of cardiovascular death or cardiovascular hospitalization, the incidence of cardiovascular

mortality, and the incidence of clinical worsening of HF did not differ between the 2 groups. Improvement in the patient-assessed dyspnea score at day 1 was seen in 74.3% of tolvaptan patients with dyspnea at baseline compared with 68.0% in the placebo group ($P < 0.001$). A mean (\pm SD) of 1.76 ± 1.91 kg weight reduction at day 1 was observed in the tolvaptan group compared with 0.97 ± 1.84 kg in the placebo group ($P < 0.001$).²⁹ Mean (\pm SD) serum Na^+ concentration increased by 5.49 ± 5.77 mEq/L at day 7 or discharge in the tolvaptan patients with low Na^+ level (<134 mEq/L) compared with 1.85 ± 5.10 mEq/L in the placebo group ($P < 0.001$). This increase was observed as early as day 1 and was maintained through 40 weeks of treatment. Mean (\pm SD) BUN levels increased by 1.94 ± 11.70 mg/dL at day 7 or discharge in the tolvaptan group compared with 3.30 ± 12.16 mg/dL in the placebo group ($P < 0.001$). This difference, favoring tolvaptan, was seen as early as day 1 and persisted long after discharge. This suggests a role for tolvaptan in patients with abnormal kidney function that limits the use of other commonly used agents that are known to worsen kidney function. Mean (\pm SD) serum creatinine level increased by 0.08 ± 0.31 mg/dL at day 7 or discharge in the tolvaptan group compared with 0.03 ± 0.35 mg/dL in the placebo group ($P < 0.001$). This difference was also seen at many of the long-term follow up points.³²

Improvement in the edema score at day 7 or discharge was significantly higher in patients with baseline pedal edema receiving tolvaptan compared with placebo ($P = 0.003$). Physician-assessed edema was significantly improved with tolvaptan as early as day 1, and maintained through post-discharge week 4. KCCQ overall summary score was not different at outpatient week 1, but statistically significant differences favoring tolvaptan were observed at the time of the last scheduled on-treatment assessment. The differences were in the quality of life domain ($P = 0.003$), the social limitation domain ($P = 0.05$), and the overall summary score ($P = 0.02$). This suggests a possible role for long-term tolvaptan therapy, although caution should be used in interpreting these findings given their tertiary nature.³²

Adverse events were noticed in 89.0% of patients on tolvaptan compared with 86.1% of placebo. The study drug was discontinued in 6.5% in the tolvaptan group compared with 5.5% in the placebo group due to adverse effects. Thirst and dry mouth were the only side effects that were observed significantly higher in the tolvaptan group ($P < 0.001$ for each).³²

In the EVEREST clinical status trials, the primary end point was a composite score of changes from baseline in

patient-assessed global clinical status and body weight at day 7 or discharge if earlier. Secondary outcomes were patient-assessed changes in dyspnea at day 1 for patients with baseline dyspnea; global clinical status at day 7 or discharge; body weight at days 1 and 7 or discharge; and peripheral edema at day 7 or discharge in patients with baseline edema.⁴²

Out of the 4133 enrolled patients, 2048 were randomized to trial A (1018 received tolvaptan, and 1030 received placebo), and 2085 to trial B (1054 received tolvaptan, and 1031 received placebo). The percentages of treatment discontinuation before day 7 (or discharge) were 2.6% and 2.4% in trial A and B, respectively. Adverse events accounted for the discontinuation of the trial in 13 patients (10 in the tolvaptan and 3 in the placebo groups) and 3 patients (2 in the tolvaptan and 1 in the placebo groups) in trial A and B, respectively. Demographic and baseline characteristics were similar between the tolvaptan and placebo groups in both trials. Mean ages ranged from 65.6 to 66.0, and males were 73% to 76%.⁴²

Tolvaptan groups had significantly greater improvement in the rank sum analysis of the composite primary outcome compared with the placebo groups; the means \pm SD were 1.06 ± 0.43 vs 0.99 ± 0.44 in trial A, and 1.07 ± 0.42 vs 0.97 ± 0.43 in trial B, respectively ($P < 0.001$ in both trials). However, no significant differences in the improvement of global clinical status at day 7 (or discharge) were observed between tolvaptan and placebo in both trials. Weight reduction was significantly higher on day 1 in the tolvaptan groups compared with placebo groups (means \pm SD were 1.71 ± 1.81 vs 0.99 ± 1.83 kg in trial A, and 1.82 ± 2.01 vs 0.95 ± 1.85 kg in trial B, respectively; $P < 0.001$ in both trials). This was also observed at day 7 (means \pm SD 3.35 ± 3.27 vs 2.73 ± 3.34 kg in trial A, and 3.77 ± 3.59 vs 2.79 ± 3.46 kg in trial B, respectively; $P < 0.001$ in both trials). Significantly higher number of patients showed improvement in their patient-assessed dyspnea score on day 1 in the tolvaptan group compared with placebo group in both trials. No statistically significant difference was noticed in the investigator-assessed pedal edema on day 7 between the tolvaptan groups and placebo groups. No significant differences in blood pressure or heart rate were observed.⁴²

In a combined post hoc analysis of the 2 trials, improvement of dyspnea and rales (over the first 4 days), and orthopnea and JVD (during the first 3 days) was higher in the tolvaptan groups compared with placebo. Alleviation of fatigue over day 3 to 6 was better achieved with tolvaptan compared with placebo ($P = 0.02$ on day 6). In patients with hyponatremia at baseline (serum Na^+ concentration < 134 mEq/L),

significantly greater correction of serum Na^+ concentration was observed with tolvaptan on day 1 and discharge. Serum K^+ , magnesium, osmolality, and creatinine were higher in the tolvaptan group, while BUN was lower. Tolvaptan patients had a mean reduction of furosemide dose from baseline greater than placebo, -55.8 and -42.9 mg/day, respectively ($P = 0.002$). An overall in-hospital mortality was 2.4% and 2.9% in the tolvaptan and placebo groups, respectively.⁴²

A post hoc analysis was performed on the EVEREST database to specifically address the effects of tolvaptan on dyspnea relief.⁴³ A 7-point Likert scale was used to measure patient-assessed dyspnea anytime on the first calendar day (day 1) following the first dose of study therapy. The timing of the patient-assessed dyspnea in relation to the first dose of study medication varied by patient (few hours post-dose to over 24 hours), and since patients were randomized within 48 hours from admission, the assessment was performed within 1 day to over 3 days from admission. During this time, background therapy aimed at relieving signs and symptoms is ongoing, which could have underestimated the significance of the results. Subgroup analysis was performed on pre-specified groups based on demographics (age, sex, and race), co-morbidities (ischemic and non-ischemic HF), baseline status (severity of edema, jugular venous distention, dyspnea, ejection fraction, and blood pressure), chemistry (BUN, serum creatinine, B-type natriuretic peptide, and serum Na^+), and in-hospital median daily furosemide dose prior to randomization.

Out of the 4133 patients in the EVEREST trial, 3664 had baseline dyspnea and were evaluated using the patient-assessed dyspnea measurement. The patients were distributed between the 2 groups; 1825 patients received tolvaptan and 1829 received placebo. Tolvaptan was associated with improvement in patient-assessed dyspnea compared with placebo (74.3% vs 68.0%, $P < 0.0001$). Dyspnea improved regardless of its severity at baseline, but the greatest improvement was seen in subjects with continuous dyspnea at baseline (75.95% and 65.65% in the tolvaptan and placebo groups, respectively, $P = 0.0021$). Dyspnea improvement with tolvaptan was modest within the first 12 hours of first dose administration, and persisted for 20 hours, but the magnitude of benefit diminished with time. Tolvaptan effects on patient-assessed dyspnea at day 1 were consistent in all of the pre-specified subgroups.

This study concluded that tolvaptan's effects on dyspnea relief were greatest within 12 hours after the first dose and emphasized the need for early randomization.

In order to assess the hemodynamic effects of tolvaptan in patients with HF New York Heart Association (NYHA)

functional class III or IV, the Efficacy of tolvaptan on hemodynamic Parameters in Subjects with heart failure (ECLIPSE) was conducted. It is a randomized, placebo controlled study, that enrolled patients with HF for at least 3 months with an ejection fraction $<40\%$, on standard HF therapy for at least 1 month. Patients with systolic blood pressure <90 mmHg, or serum creatinine ≥ 3 mg/dL were excluded.⁴⁴

Before randomization, patients entered a baseline inpatient phase, during which they received their daily dose of concomitant background medications, and then 2 hours later, a pulmonary artery catheter was inserted. Afterwards, patients entered into 2 to 20-hour stabilization period, after which the pulmonary capillary wedge pressure (PCWP) was measured. Patients were eligible for randomization if their PCWP was >18 mmHg on 2 successive readings at least 10 minutes apart and were randomized within 2 hours to receive tolvaptan 15, 30, or 60 mg, or placebo in 1:1:1:1 ratio. Those patients have advanced symptomatic HF with abnormal baseline hemodynamics, so generalizability of these data to all patients with HF is not certain. Hemodynamic and renal parameters were assessed at multiple points over an 8-hour assessment period during which the background diuretics and HF medications were stopped and fluid intake was restricted to 250 mL every 2 hours.

The primary efficacy end point was the peak change in PCWP from baseline within 3 to 8 hours after drug administration. Secondary efficacy end points included AUC for the change from baseline in PCWP and other hemodynamic parameters over the 8-hour evaluation period and renal and electrolyte parameters. A total of 181 patients were randomized; 44, 43, 46, and 48 patients received tolvaptan 15, 30, or 60 mg, or placebo, respectively. The mean (\pm SD) ages were 60.3 ± 11.7 , 59.7 ± 13.4 , 61.0 ± 11.9 , and 58.9 ± 14.0 in the tolvaptan 15, 30, and 60 mg, and placebo groups, respectively. Males were 72.7%, 83.7%, 78.3%, and 83.3% in the tolvaptan 15, 30, and 60 mg, and placebo groups, respectively.

Tolvaptan showed a statistically significant decrease in peak change in PCWP from 3 to 8 hours after drug administration as compared with placebo; the means \pm SD were -6.38 ± 4.12 ($P = 0.003$), 15.67 ± 4.58 ($P = 0.044$), -5.71 ± 4.35 ($P = 0.033$), and -4.16 ± 4.57 , in the tolvaptan 15, 30, and 60 mg, and placebo, respectively. The AUC for the change from baseline in PCWP over the 8-hour evaluation period was showing a statistically significant difference with only the 15 mg tolvaptan compared with placebo. All tolvaptan doses produced statistically significantly greater

changes in peak change in pulmonary artery pressure as compared with placebo, but only the 15 and 30 mg doses resulted in statistically significant reductions in peak change in right atrial pressure. This reduction in right atrial pressure is related to volume loss from the increased urine output, which can explain the improvement in dyspnea at day 1 after tolvaptan administration that was noticed in the EVEREST trial. No significant changes in cardiac index, pulmonary vascular resistance, and systemic vascular resistance were observed.⁴¹

A dose-dependent increase in urine output was observed with tolvaptan ($P < 0.0001$ for all tolvaptan groups vs placebo), and urine osmolality was significantly lower with all tolvaptan doses as compared with placebo ($P < 0.0001$). Significantly higher free water clearance was observed with all tolvaptan doses. Plasma osmolality showed significantly small increase with all tolvaptan doses. A dose-related modest increase in serum Na^+ concentration (mean \pm SD) was observed with tolvaptan 15 (1.2 ± 2.5 mEq/L), 30 (3.3 ± 3.9 mEq/L), and 60 mg (4.6 ± 4.9 mEq/L), as compared with placebo group (-0.7 ± 3.2 mEq/L). No significant changes in serum creatinine, BUN, K^+ , and vital signs were observed. Tolvaptan therapy was well tolerated during this study, and there were no drug-related deaths.⁴¹

This study showed that tolvaptan administration was associated with modest favorable changes in hemodynamics in patients with advanced HF.⁴⁴

The potential beneficial effect of tolvaptan on remodeling was assessed in the Multicenter Evaluation of Tolvaptan Effect on Remodeling (METEOR) study, which was a multicenter, randomized, double-blind, placebo-controlled study. It evaluated the effects of long-term administration of 30 mg/day of tolvaptan on left ventricular end-diastolic volume (LVEDV) in patients with HF and reduced systolic function. LVEDV was assessed by quantitative radionuclide ventriculography at baseline, after 1 year of therapy, and 7 days after study drug withdrawal.⁴⁵

Patients included in the study were NYHA functional class II to III HF, with an ejection fraction $\leq 30\%$ within 1 year from randomization, on standard HF therapy for at least 3 months, and with a stable dose for 2 weeks prior to enrollment.

A total of 240 patients were enrolled. The patients were randomized to receive tolvaptan (120), or placebo (120). Mean (\pm SD) age was 65 ± 12 and 63 ± 12 years in the tolvaptan and placebo groups, respectively. Men were 82% and 81% in tolvaptan and placebo groups respectively. Out of the 120 patients in each group, 91 and 89 patients

completed the study in the tolvaptan and placebo groups, respectively. At baseline, LVEDV index, left ventricular end systolic volume (LVESV) index, and left ventricular ejection fraction were similar between the tolvaptan and placebo groups. At 1 year, the mean (\pm SD) changes in LVEDV index were -1.78 ± 10.7 and 0.04 ± 10.0 mL/m², in the tolvaptan and placebo groups, respectively ($P = 0.21$). There was also no difference in LVED index between the 2 groups 1 week after study drug withdrawal.

Changes in LVESV index and left ventricular ejection fraction were pre-specified secondary end points in this study. None of them was different in tolvaptan group as compared with placebo group at 1 year, and 1 week after study drug withdrawal. No difference was seen in blood pressure, heart rate, serum Na⁺, K⁺, BUN, and creatinine between the 2 groups. No statistically significant differences in the Minnesota Living With Heart Failure Questionnaire score, Visual Analog Scale assessment of global status, respiratory status, subject-assessed overall treatment effect, and patient-assessed global status were noticed between the tolvaptan and placebo groups.

Other outcomes were looked at, such as mortality and neurohormonal effects of tolvaptan, however they were not pre-specified. In the tolvaptan group, 5% death rate, and 18% HF hospitalization rate were observed, compared with 9% and 28% in the placebo group, respectively. In a time-to-event analysis, the composite of mortality or HF hospitalization favored tolvaptan ($P < 0.03$). AVP levels increased with tolvaptan treatment as compared with placebo. However, BNP levels decreased with tolvaptan and placebo, with a larger, statistically insignificant, decrease in the tolvaptan group. Urinary frequency, thirst, and dry mouth were more commonly reported with tolvaptan treatment in this trial.

This trial demonstrated that tolvaptan therapy had no significant effect on left ventricular remodeling.⁴² Although the outcome was disappointing as the hope for reversed remodeling did not materialize, it alleviated the concern that using selective V₂ receptor antagonist might have a deleterious effect from abundant AVP stimulating V₁ receptors, that could potentially result in vasoconstriction and deleterious remodeling.

The effect of tolvaptan on renal hemodynamics, water excretion, and neurohormones as compared to diuretic was assessed in a randomized, placebo-controlled crossover study, in which 14 patients with chronic HF NYHA functional class II-III, and left ventricular ejection fraction $<40\%$ within 1 year prior to enrollment were enrolled.⁴⁶ Mean (\pm SD) age was 56 ± 8 years, and men were 71%. The patients were

placed on 2 g/day Na⁺ diet and ACEI (other than captopril) were discontinued and replaced with captopril 15 days before the start of the study. Patients were admitted 3 days prior to the study and captopril, diuretics, β -blockers, and aspirin were discontinued. On day 1, patients received either a single dose of placebo or 30 mg tolvaptan and were crossed over to furosemide on day 3. On day 5, all patients received 80 mg of furosemide. Day 2 and 4 were washout days.

Significant increases in the urine flow were noticed with tolvaptan and furosemide compared with placebo ($P < 0.05$), but there was no difference between the 2 medications. Urinary Na⁺ excretion, Na⁺ clearance, K⁺ excretion, and K⁺ clearance were significantly higher with furosemide compared with placebo ($P < 0.05$) and tolvaptan ($P < 0.05$), and there was no difference between the latter 2. Urine osmolality decreased with tolvaptan as compared with placebo ($P < 0.05$), and tended to be lower compared with furosemide ($P = 0.10$). Renal blood flow and distal fractional reabsorption of Na⁺ were significantly lower with furosemide compared with placebo ($P < 0.05$) and tolvaptan ($P < 0.05$), with no difference between the latter 2 ($P = 0.19$). Effective renal plasma flow tended to be lower with furosemide compared with placebo and tolvaptan ($P = 0.053$). There were no differences between the 3 groups in mean arterial pressure, heart rate, glomerular filtration rate, renal vascular resistance, and proximal fractional reabsorption of Na⁺.

No significant changes in plasma Na⁺ levels were seen with tolvaptan and a trend for a decrease was noted with furosemide. No significant differences in serum K⁺ concentration were noticed between the groups. Statistically significant increases in plasma renin activity and norepinephrine were seen with furosemide compared with placebo.

This study demonstrates that tolvaptan enhanced aquaresis in HF without adversely affecting hemodynamics, urinary Na⁺ or K⁺ excretion, serum electrolytes, or neurohumoral activation.

Conclusion

Based on the preceding review of the clinical experience with tolvaptan, its efficacy in correcting hyponatremia in patients with euvolemic or hypervolemic hyponatremia is clearly established. The available data on the safety of tolvaptan should provide health care providers the needed comfort for prescribing it although a larger experience is still required.

The unique aquaretic property of tolvaptan, as a V₂ receptor antagonist, combined with the evidence documenting sustained weight loss in patients with HF and hypervolemia make

it an attractive option for the management of hypervolemic hyponatremia. Theoretically, activation of V_1 receptors by the abundant AVP may lead to increased systemic vascular resistance and hemodynamic deterioration. However, the lack of detrimental effect by tolvaptan on remodeling in patients with systolic HF and the neutral effect on outcomes should alleviate the concern that the use of selective V_2 receptor antagonists in systolic HF may not be advisable. The concern that the use of selective V_2 receptor antagonist may be detrimental in HF has been alleviated.

Despite the neutral effect of tolvaptan on outcomes among patients with systolic HF the available safety records provide a basis for its use to correct moderate to severe hyponatremia among outpatients with systolic HF. The decision to prescribe tolvaptan in this setting is not based on any evidence of improvement in symptoms or outcome but largely dictated by the comfort level of health care providers. The notion that in patients with systolic HF and volume overload, tolvaptan may provide benefit by either replacing or reducing the dose of diuretics is not supported by the available data. The lack of neurohormonal activation, however, combined with the lack of a negative effect on electrolytes support further research effort for this indication.

It should be clearly acknowledged that failure of tolvaptan to improve outcome among patients hospitalized with decompensated systolic HF may entirely be explained by failure to target hyponatremic patients. Thus, the potential beneficial effects of tolvaptan in improving outcomes in patients with decompensated HF associated with hyponatremia have not been explored yet.

Disclosure

The authors declare no conflicts of interest.

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