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Efficacy and Safety of Tolvaptan in Patients Hospitalized With Acute Heart Failure

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ABSTRACT

BACKGROUND The oral vasopressin-2 receptor antagonist tolvaptan causes aquaresis in patients with volume overload, potentially facilitating decongestion and improving the clinical course of patients with acute heart failure (AHF).

OBJECTIVES The TACTICS-HF (Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure) study was conducted to address the acute use of tolvaptan to improve congestion in AHF.

METHODS The TACTICS-HF study randomized patients (n = 257) within 24 h of AHF presentation in a prospective, double blind, placebo-controlled trial. Patients were eligible regardless of ejection fraction, and were randomized to either 30 mg of tolvaptan or placebo given at 0, 24, and 48 h, with a fixed-dose furosemide regimen as background therapy. The primary endpoint was the proportion of patients considered responders at 24 h. Secondary endpoints included symptom improvement, changes in renal function, and clinical events.

RESULTS Dyspnea relief by Likert scale was similar between groups at 8 h (25% moderately or markedly improved with tolvaptan vs. 28% placebo; p = 0.59) and at 24 h (50% tolvaptan vs. 47% placebo; p = 0.80). Need for rescue therapy was also similar at 24 h (21% tolvaptan, 18% placebo; p = 0.57). The proportion defined as responders at 24 h (primary study endpoint) was 16% for tolvaptan and 20% for placebo (p = 0.32). Tolvaptan resulted in greater weight loss and net fluid loss compared with placebo, but tolvaptan-treated patients were more likely to experience worsening renal function during treatment. There were no differences in in-hospital or post-discharge clinical outcomes.

CONCLUSIONS In patients hospitalized with AHF, dyspnea, and congestion, the addition of tolvaptan to a standardized furosemide regimen did not improve the number of responders at 24 h, despite greater weight loss and fluid loss. (Targeting Acute Congestion With Tolvaptan in Congestive Heart Failure [TACTICS-HF]; NCT01644331) (J Am Coll Cardiol 2017;69:1399–406) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure

BNP = B-type natriuretic peptide

HF = heart failure

IV = intravenous

Elevated ventricular filling pressures (i.e., congestion) are the primary reasons for hospitalization in patients with heart failure (HF) (1). In the setting of acute heart failure (AHF), congestion leads to worsening symptoms (typically dyspnea) and contributes to end-organ dysfunction (2). Despite the use of diuretic agents and vasodilators targeting decongestion, congestion persists in many patients with AHF at hospital discharge and has been associated with increased morbidity and mortality (3). Many patients with AHF are relatively resistant to the effect of loop diuretic agents, particularly patients with chronic kidney disease and hyponatremia (4). Adjunctive therapies such as nesiritide or low-dose dopamine were not found to enhance decongestion or improve renal function in patients with AHF (5). Alternative nonpharmacological treatments for fluid removal, such as ultrafiltration, may further compromise renal function and have generally not improved clinical outcomes (6). Collectively, these data suggest the need to identify therapies that can effectively and safely treat congestion in patients with AHF.

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The oral vasopressin-2 receptor antagonist tolvaptan inhibits the action of antidiuretic hormone and leads to the loss of free water (aquaresis) in patients with HF (7). Tolvaptan is currently approved by the Food and Drug Administration for the treatment of clinically significant hyponatremia, which is seen in some HF patients, or as part of inappropriate antidiuretic hormone secretion syndrome. The large-scale EVEREST (Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with Tolvaptan) trial did not demonstrate superiority of tolvaptan over placebo in terms of long-term clinical outcomes (8), although potentially beneficial effects on volume status and AHF symptoms were observed in the initial treatment days (9,10). In post hoc analyses, patients with lower serum sodium (and presumably greater activation of the arginine vasopressin axis) were more likely to show improvement with tolvaptan versus placebo (11). Additionally, patients randomized relatively early during their hospitalization were more likely to show improvement in symptoms with tolvaptan (10). These data suggest that in select AHF patients, early treatment with tolvaptan in addition to loop diuretic agents may improve congestion and, therefore, may improve the symptoms of AHF. Our study, TACTICS-HF (Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure) (NCT01644331), tests this hypothesis.

METHODS

STUDY DESIGN. The detailed design of the TACTICS-HF study has been published previously (12). Briefly, TACTICS-HF was a randomized, double blind, placebo-controlled, multicenter clinical trial of 30 mg of oral tolvaptan versus placebo given at 0, 24, and 48 h (i.e., 3 doses) in patients hospitalized for AHF and congestion. The study was designed and conducted by an independent academic steering committee, and funded by Otsuka Pharmaceuticals. The Data Coordinating Center (Duke Clinical Research Institute) was responsible for data management and statistical analysis. An independent Data Safety and Monitoring Committee monitored the trial conduct and the safety of study participants. The study was approved by the institutional review board at each study site, and all patients provided written informed consent.

STUDY PARTICIPANTS. Patients were eligible if they presented within the previous 24 h with AHF and had dyspnea at rest or with minimal exertion, elevated natriuretic peptide levels (B-type natriuretic peptide [BNP] >400 pg/ml or amino-terminal BNP >2,000 pg/ml), and at least 1 additional sign or symptom of congestion (orthopnea, edema, elevated jugular venous pulse, rales, or congestion on chest radiograph). There was no ejection fraction criterion, and patients could be enrolled whether they had HF with reduced ejection fraction or HF with preserved ejection fraction. Patients were required to have a serum sodium of ≤140 mmol/l at the time of randomization. Patients were also required to have a daily oral diuretic requirement of 40 mg of furosemide (or equivalent) prior to presentation. We excluded those with hypotension (systolic blood pressure <90 mm Hg), severe renal dysfunction (serum creatinine >3.5 mg/dl or requiring renal replacement therapy), and those receiving intravenous (IV) vasoactive therapy (vasodilators or inotropic agents) or ultrafiltration.

RANDOMIZATION AND TREATMENT ASSIGNMENT. Patients were randomly assigned in a 1:1 blinded fashion to either oral tolvaptan (30 mg taken by mouth at 0, 24, and 48 h) or matching placebo. All patients received a standardized loop diuretic regimen for the first 48 h from randomization consisting of IV furosemide equivalent to their total daily oral outpatient dose (in furosemide equivalents) administered in divided doses every 12 h (or 40 mg IV furosemide every 12 h, if greater). This regimen mirrored the "low dose" arm in the DOSE (Diuretic Optimization Strategies Evaluation) study (13) and