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EDITORIAL

Is Intravenously Administered Tolvaptan Mighty Like Triton?

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Heart failure (HF) is a global public health burden as shown by high prevalence and mortality rates.[1] In patients with HF, diuretics are essential and widely used for the relief of congestion through achieving a state of euvolaemia.[2] However, several studies have reported that the high-dose loop diuretic, furosemide, is associated with worsening renal function and may be harmful for HF patients' prognosis.[3–5] Furthermore, when

Article p????

treating patients with the acute phase of congestive HF, a time-sensitive approach with diuretics is critical.[6–8] When furosemide is ineffective, then the alternative is to increase the dose of furosemide or combine it with other diuretics,[6] including tolvaptan.[7] Of note, in a Japanese nationwide

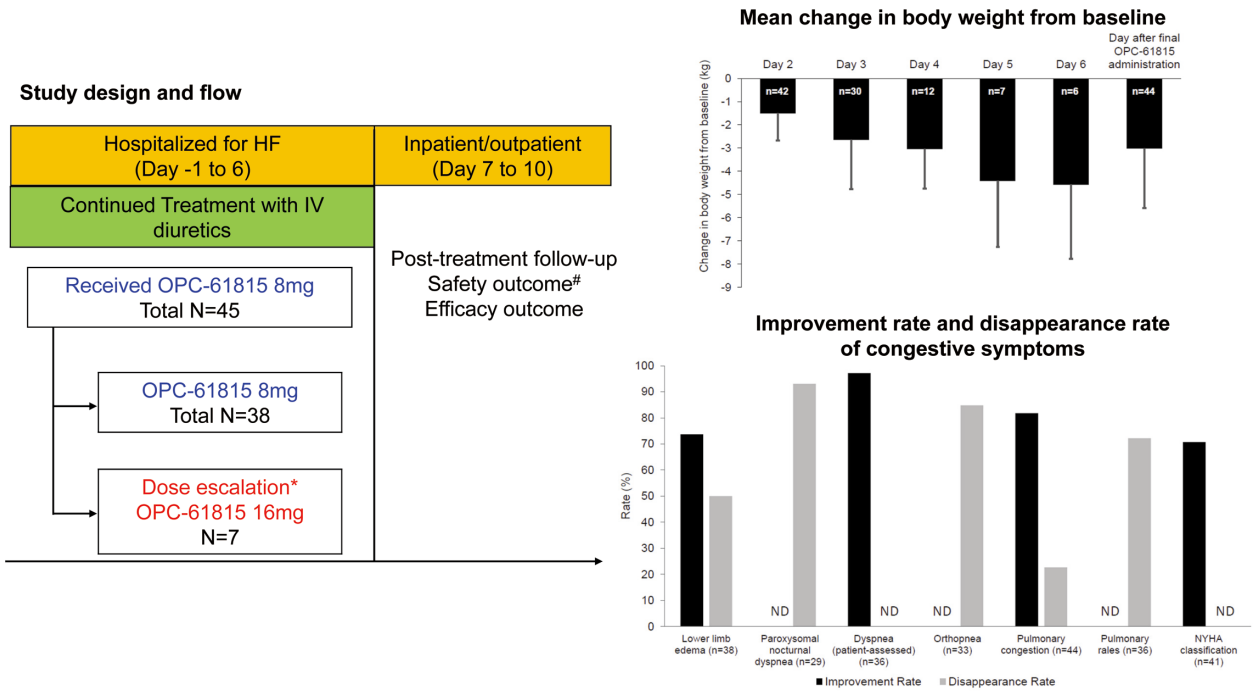

Figure. Design and results of TRITON-HF, a phase III multicenter open-label trial. *Eligibility for dose escalation was assessed on Day 2 of the treatment period (and Day 3, if applicable). Dose escalation criteria were as follows: Inadequate response, serum sodium concentration of ≤147 mEq/L at 8 mg, no evident increase of >10 mEq/L in serum sodium concentration within 24 h of the start of OPC-61815 administration, and no safety concerns. #Most treatment-emergent adverse events were mild or moderate in severity. ND, no data. (Reproduced with permission from Kinugawa K, et al.[10])

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HF database, tolvaptan was prescribed in >40% of patients hospitalized with HF, of whom >50% received tolvaptan within 2 days of hospitalization.[9] However, in the clinical setting, oral tolvaptan administration is limited when the HF patient has impaired consciousness, is being ventilated, at high risk of aspiration, or has impaired swallowing reflex, requiring intravenously administered tolvaptan.

The TRITON-HF (ToleRability of the Intravenously administered TOlvaptaN prodrug OPC-61815 in patients with congestive Heart Failure who have difficulty with or are incapable of oral intake), a phase III, multicenter, open-label trial by Kinugawa and colleagues,[10] the results of which are now published in the Journal, is the first to confirm the tolerability of once-daily intravenous OPC-61815 (8 or 16 mg) for a maximum of 5 days in HF patients who have volume overload despite having received injectable diuretics (other than vasopressin antagonists) and who had difficulty with or were incapable of oral intake. In this trial of intravenous OPC-61815 treatment, the investigators found that OPC-61815 was well tolerated, and its previously reported safety and efficacy were confirmed in HF patients for whom oral intake was difficult or impossible. In fact, most treatment-emergent adverse events (TEAEs) were mild or moderate in severity given that the most frequently reported TEAE was constipation in 12 (26.7%) patients and the most frequently reported treatment-related TEAE was dry mouth in 2 (4.4%) patients. Serious TEAEs were reported in 2 (4.4%) patients (ventricular tachycardia and pleural effusion in 1 patient each). Furthermore, treatment resulted in weight decrease (−3.01 kg); improvement or disappearance rates for other congestive HF symptoms implied that treatment was effective. Furthermore, urine excretion was increased 0–1 h after OPC-61815 administration and reached a maximum level at 1–2 h (**Figure**).

In daily practice, who will be the target for this new weapon against HF? The trial inclusion criteria would be a clue; that is, diagnosed with congestive HF with volume overload despite treatment with injectable diuretics and oral intake judged to be difficult or impossible. Given the information that ongoing non-invasive positive pressure ventilation (NPPV) therapy (57.8%) and risk of aspiration (31.1%) were the reasons for participation in the trial, we may need to start OPC-61815 administration in HF patients with NPPV or at risk of aspiration and with diuretic resistance. Notably, regardless of concomitant use of catecholamines, blood pressure and heart rate were not changed significantly after OPC-61815 injection, suggesting an acceptable safety profile in a broad spectrum of HF. As the authors acknowledge in the limitations, few patients met the dose increase criteria and had the dose increased to 16 mg; therefore, the findings for the 16-mg group should be interpreted with caution. In addition, there was no comparator group in the trial, calling for further research to confirm efficacy and safety of OPC-61815 in HF patients.

Disclosure

None.

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