

Oral vasopressin receptor antagonist tolvaptan in right heart failure due to pulmonary hypertension

To the Editor:

During the past decade, the prognosis of patients with pulmonary hypertension (PH) has improved due to the development of pulmonary arterial vasodilators [1]. Yet, treatment for right-sided heart failure (RHF) associated with PH has not improved, despite being the most important prognostic factor for chronic RHF [2, 3]. Existing treatment strategies for RHF associated with PH are restricted to administration of loop diuretics and inotropes [4]; however, administration of high doses of loop diuretics may worsen the outcome of chronic heart failure [5, 6]. In recent years, tolvaptan, an oral, nonpeptide, selective vasopressin V2-receptor antagonist, has been developed for the treatment of hyponatraemia [7], autosomal dominant polycystic kidney disease [8] and heart failure. Used in addition to standard therapy that includes diuretics, tolvaptan improves many signs and symptoms of heart failure without serious adverse events [9]. However, there is no report describing the effect of tolvaptan on RHF, independent of left-sided heart disease.

We evaluated both the short- and long-term effects of tolvaptan, and explored the possibility of loop diuretics dose reduction and improved fluid retention in patients with refractory and loop diuretics-dependent RHF associated with PH.

We enrolled 10 outpatients with chronic RHF associated with PH, who were refractory to loop diuretics, between September 2012 and March 2014 at Keio University Hospital (Tokyo, Japan). This study was an open-label, single-arm, prospective study to investigate the safety and efficacy of tolvaptan in patients with RHF due to PH. The study consisted of a 12-week open-label treatment period with tolvaptan (with visits at baseline, days 1–7, and weeks 2, 4, 6 and 12), and followed the ethical standards of the responsible committee on human experimentation (Keio University School of Medicine ethical committee, Tokyo, Japan) and the Helsinki Declaration. The trial was registered at UMIN before initiating recruitment (identifier number: UMIN000010196). Written informed consent was obtained from all patients in the study. All patients had been previously diagnosed as having idiopathic pulmonary arterial hypertension (IPAH) (n=5) or chronic thromboembolic pulmonary hypertension (CTEPH) (n=5), as confirmed by right heart catheterisation. The baseline dose of furosemide was 60 mg·day⁻¹ for more than 4 weeks and patients were also taking specific therapies for PH such as oral phosphodiesterase type-5 inhibitors and/or endothelin receptor antagonists. All patients were free from defects such as a predominant left-to-right shunt or any other kind of cardiomyopathy (e.g. ischaemic cardiomyopathy or valvular heart disease). The mean±SD age of the patients was 47.8±15.6 years and the number of females was five (50%). Each patient had been receiving loop diuretics, with an average furosemide dose of 88±17 mg·day⁻¹. None of the patients had taken another type of diuretic such as spironolactone or hydrochlorothiazide.

The primary end-point was a changed furosemide dosage at week 12 relative to baseline. Tolvaptan was administered orally at a dose of 3.75 mg, 7.5 mg or 15 mg per day. For safety reasons, all participants commenced tolvaptan at a dose of 3.75 mg·day⁻¹ for 3 days. Provided urine output did not increase during this initial 3-day period, the dosage of tolvaptan was increased to 7.5 mg·day⁻¹ and 15 mg·day⁻¹. The dosage of furosemide was reduced in cases satisfying the following conditions: 1) urine output was greater than baseline levels, and more than 1000 mL per day; and 2) there was no evidence of increased body weight compared with the previous day. In cases free from increased fluid retention (leg oedema, hepatomegaly or jugular vein distention), a reduction of furosemide would be considered from 160 mg, 120 mg, 80 mg, 60 mg, 40 mg, 20 mg, to 10 mg per day.

The mean±SD dosage of tolvaptan at day 7 and week 12 were 6.38±1.8 mg·day⁻¹ and 7.87±4.1 mg·day⁻¹, respectively. During the adjustment of tolvaptan dosing, neither overcorrection of serum sodium (>150 mEq·L⁻¹) or elevated liver enzymes were noted, and the main adverse event was a dry mouth (80%). There were no withdrawals from the study due to adverse events. There were no patients who developed hypotension or experienced worsening heart failure during treatment.

The comparisons of clinical variables at baseline and post-tolvaptan treatment are shown in figure 1. The mean dose of furosemide administered at day 7 and week 12 compared with baseline was significantly reduced by tolvaptan treatment (p=0.001). Tolvaptan was also associated with a significant decrease in average urine osmolality and brain natriuretic peptide levels at week 12 compared with baseline (p=0.001

and $p=0.014$, respectively). Improvements in physical assessments (body weight, leg oedema and jugular vein distention) were also associated with tolavaptan treatment. Serum sodium, potassium and creatinine concentrations showed no significant changes during the time course of the treatment. Blood pressure and heart rate remained unchanged during treatment. The effect of the study drugs on self-assessed health

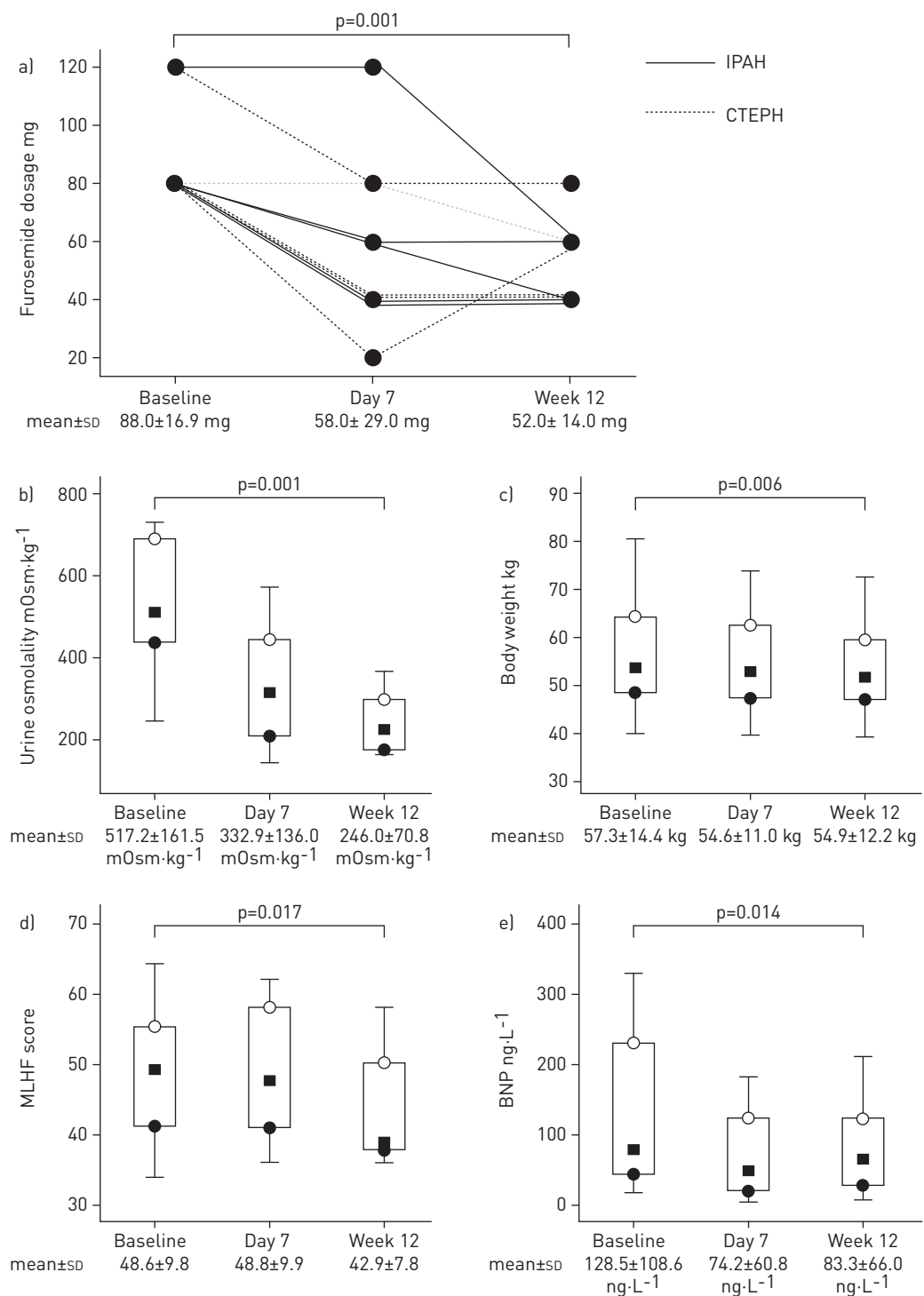


FIGURE 1 a) Line graphs of furosemide dosage in each patient during tolavaptan treatment. Box and whisker plots of b) urine osmolality, c) body weight, d) Minnesota Living with Heart Failure Questionnaire (MLHF) score, and e) brain natriuretic peptide (BNP) at baseline, day 7 and week 12 after commencement of tolavaptan treatment. Squares represent the mean, circles represent the 25th and 75th percentiles, and whiskers represent the range. IPAH: idiopathic pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension.

status was determined using the Minnesota Living with Heart Failure Questionnaire (MLHF), and the average score was significantly improved ($p=0.017$).

All data are expressed as mean \pm SD. Patients who took at least one dose of tolvaptan were included in the set for analyses. A comparison of data obtained at baseline, day 7 and week 12 was made using the nonparametric Friedman's test. The significance level in all statistical analyses was set at 5% (two-sided). All analyses were performed using SPSS statistical software (version 20.0; IBM Corp., Armonk, NY, USA).

From these results, tolvaptan treatment achieved a significant reduction in furosemide dosage over a 12-week period in patients with chronic RHF associated with PH, and did so without any serious adverse events. In addition, tolvaptan administration also produced significantly improved brain natriuretic peptide levels and physical findings of fluid retention associated with a decrease in urine osmolality.

While RHF is an established risk factor for a poor prognosis in patients with PH, there is no established treatment for targeting RHF itself. Digoxin was tested in a small study of 17 patients with pulmonary arterial hypertension (PAH), which suggested digoxin has acute haemodynamic effects [10]. In a basic study, NAGENDRAN *et al.* [11] demonstrated that sildenafil may have direct inotropic effects. Use of high-dose loop diuretics is unavoidable in the treatment of fluid retention in classical RHF associated with PH. However, use of these diuretics is accompanied by a poor prognosis and worsening renal failure due to upregulation of the renin-angiotensin-aldosterone system and sympathetic nerve activation in patients with chronic heart failure [9]. In such cases, the vasopressin type 2-receptor selective antagonist, tolvaptan, is considered a potent therapy, because the upregulation of vasopressin is associated with the aggravation of the renin-angiotensin-aldosterone system [12]. Excess vasopressin produces fluid retention *via* a direct effect on the renal collecting duct in patients with chronic heart failure. As a result of a continuous vasopressin excess, circulating blood volume and urine osmolality will increase, even if using high-dose loop diuretics. This phenomenon is known as loop diuretics resistance [13].

We expect tolvaptan has the potential to become the first potent drug leading to long-term survival benefits in patients with RHF due to PH, for whom there is currently no established treatment. This study is prospective, and is a small single-armed pilot study lacking long-term observations. However, its positive results suggest that there should be no hesitation to pursue further investigation in a multicentre randomised control study and confirm the beneficial effects of tolvaptan in this type of patient.



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Vasopressin receptor antagonist tolvaptan achieved furosemide reductions and right heart failure improvements in PH <http://ow.ly/Lopej>

Yuichi Tamura^{1,2,3,4}, Mai Kimura¹, Makoto Takei¹, Tomohiko Ono¹, Masataka Kuwana⁵, Toru Satoh⁶, Keiichi Fukuda¹ and Marc Humbert^{2,3,4}

¹Dept of Cardiology, Keio University School of Medicine, Tokyo, Japan. ²Faculté de Médecine, Université Paris-Sud, Le Kremlin Bicêtre, France. ³Service de Pneumologie, DHU Thorax Innovation, Hôpital Bicêtre, Assistance Publique Hôpitaux de Paris, Le Kremlin-Bicêtre, France. ⁴Inserm UMR_S 999, LabExLERMIT, Centre Chirurgical Marie Lannelongue, Le Plessis Robinson, France. ⁵Dept of Allergy and Rheumatology, Nippon Medical School, Tokyo, Japan. ⁶Dept of Cardiology, Kyorin University School of Medicine, Tokyo, Japan.

Correspondence: Yuichi Tamura, Dept of Cardiology, Keio University School of Medicine, 35 Shinanomachi Shinjuku-ku, Tokyo 160-8582, Japan. E-mail: u1@ta-mu.net

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