

The role of tolvaptan in pulmonary hypertension

A retrospective study

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Abstract

Pulmonary hypertension (PH) is a severe form of pulmonary vascular disease that can lead to right heart failure (RHF). Nearly 2-thirds of patients with PH die within 5 years. Studies suggest that a new diuretic medication, called tolvaptan (TLV), can be used to treat PH. However, there is still insufficient evidence to confirm its effectiveness. Therefore, we investigated the role of TLV in patients with PH. This retrospective study included 73 patients with PH hospitalized in Shanghai Pulmonary Hospital between November 2019 and March 2022. All patients received 7.5 to 15.0 mg of TLV for 3 to 21 days starting at admission, in addition to targeted drugs and traditional diuretic therapy. The outcomes included the blood pressure, urine and water intake volumes, electrolyte concentrations, and renal, liver, and cardiac function indexes before and after TLV treatment. In addition, we assessed the clinical symptoms and adverse reactions during the treatment. After TLV treatment, the water intake and urine volumes significantly increased, and body weight, diastolic blood pressure (DBP) and mean arterial pressure significantly decreased. Total bilirubin, direct bilirubin, N-terminal pro-brain natriuretic peptide, and serum uric acid (UA) levels after TLV treatment were significantly lower than before treatment. After TLV treatment, dyspnea significantly improved in 71 of 73 patients, and lower limb edema disappeared in 42 of 53 patients. No obvious adverse reactions occurred during the TLV treatment period. These results suggest that adding TLV to targeted drug and traditional diuretic therapies is effective for patients with PH. However, more data are required to support these findings.

Abbreviations: DBIL = direct bilirubin, DBP = diastolic blood pressure, NT-proBNP = N-terminal pro-brain natriuretic peptide, PAH = pulmonary arterial hypertension, PH = pulmonary hypertension, RHF = right heart failure, TBIL = total bilirubin, TLV = tolvaptan, UA = uric acid, WHO = World Health Organization.

Keywords: effectiveness, pulmonary hypertension, right heart failure, tolvaptan

1. Introduction

Pulmonary hypertension (PH) is a progressive disorder characterized by a chronic increase in pulmonary arterial pressure, frequently resulting in right heart failure (RHF) and potentially death.^[1] PH is relatively common, affecting approximately 1% of all adults globally and 10% of those aged over 65 years.^[2] The most recent the World Symposium on PH was modifying the clinical classification of PH into 5 groups: Group 1 is pulmonary arterial hypertension (PAH); Group 2 PH includes patients who have left hearts disease; Group 3 includes those who chronic lung diseases and/or hypoxia; Group 4 patients have pulmonary artery obstructions, including chronic thromboembolic PH; Group 5 is composed of a heterogenous group with unknown of multifactorial mechanisms of PH development.^[3]

Tolvaptan (TLV) is an oral selective vasopressin type 2 receptor antagonist that inhibits vasopressin binding and increases the electrolyte-water clearance rate.^[4] Some studies have demonstrated that TLV causes adverse reactions, such as a rapidly

increasing serum sodium level.^[5,6] Nonetheless, TLV has been widely used to treat hyponatremia, autosomal dominant polycystic kidney disease, and heart failure.^[7-9]

Moreover, 1 study treated patients with PH-induced RHF with TLV for 12 weeks, finding that their weight decreased significantly, heart failure symptoms improved, and there were no obvious adverse reactions or hypernatremia^[10] However, using TLV for PH-induced RHF is still in the preliminary testing stage, and its safety and effectiveness have not been fully confirmed. Therefore, this study retrospectively analyzed correlations between the clinical indications of patients with PH and TLV in our hospital to provide some basis for TLV as a PH treatment.

2. Methods

2.1. Patients

We retrospectively analyzed the relevant clinical data of patients with PH from Shanghai Pulmonary Hospital.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]

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Patients ≥ 18 years old diagnosed with PH by right heart catheterization were included. Furthermore, all included patients were administered 7.5 to 15 mg of TLV for 3 to 21 days starting at admission, in addition to targeted drug and traditional diuretic therapies. Patients with malignant tumors, severe liver dysfunction, severe kidney dysfunction, or incomplete records were excluded. We screened 136 patients, and 73 were enrolled based on the inclusion and exclusion criteria. The flow diagram of the retrospective analysis was presented in Figure 1.

2.2. Ethical approval

Shanghai Pulmonary Hospital approved the experimental design.

2.3. Data collections

We retrospectively collected the following data from the patients' medical records: sex, age, height, body weight, alcohol consumption, smoking, mean pulmonary artery pressure, clinical classification of PH, the World Health Organization functional class, and hemoglobin, alanine transaminase, aspartate aminotransferase, total bilirubin (TBIL), direct bilirubin (DBIL), total bile acid, uric acid (UA), blood urea nitrogen, serum creatinine, Cystatin C, N-terminal pro-brain natriuretic peptide (NT-proBNP), the levels of potassium, sodium, chloride, and calcium, and heart rate, blood pressure, water intake, urine volume.

Two authors used a standardized form to gather patient-related information; the 2 result sets were checked against each other to ensure accuracy and reduce the risk of bias.

2.4. Statistical analyses

In the study, GraphPad Prism 5.01 software was adopted for statistical analysis of experiment data. Measurement data were expressed as mean \pm standard deviation (SD); comparison between the 2 groups was tested by *t* test. In this study, $P < .05$ indicated statistical difference.

3. Results

Table 1 presents the baseline characteristics of the enrolled patients ($n = 73$); 68.49% patients were women. The mean age was 54.29 ± 15.68 (range, 22–83) years, and 31.51% patients were older than 65 years. The mean body mass index was 21.28 ± 0.49 kg/m². Three patients (4.11%) were found to have long-term alcohol drinking, 7 patients (9.659%) were found to have long-term smoking. The mean pulmonary artery pressure

range of the enrolled patients was 27 to 108 mm Hg. Of all patients, 35 patients (47%) were found to have WHO group 1 PH, 4 patients (5.48%) were found to have WHO group 2 PH, 9 patients (12.33%) were found to have WHO group 3 PH, 7 patients (9.59%) were found to have WHO group 4 PH, 18 patients (24.66%) were found to have WHO group 5 PH. Sixty-seven PH patients (91.78%) were World Health Organization functional class III/IV in our study.

Most clinical indicators were comparable before and after TLV treatment (Table 2). The TBIL, DBIL, NT-proBNP, and serum UA levels were significantly lower after TVL treatment. TBIL level decreased from 31.86 ± 3.79 μ mol/L to 24.67 ± 2.55 μ mol/L ($P = .001$), DBIL level decreased from 16.34 ± 2.60 μ mol/L to 13.49 ± 1.88 μ mol/L ($P = .018$), NT-proBNP level decreased from 4396 ± 594.90 pg/mL to 2974 ± 437.00 pg/mL ($P = .023$), serum UA level decreased from 526.9 ± 22.99 μ mol/L to 445.3 ± 26.18 μ mol/L ($P < .0001$). However, serum potassium level significantly increased from 4.03 ± 0.07 mmol/L to 4.27 ± 0.06 mmol/L ($P = .002$) after TVL treatment than before TLV treatment. Other serum biomarker levels did not differ before and after treatment.

Furthermore, the diastolic blood pressure (DBP) and mean arterial pressure significantly decreased after TVL treatment (all $P < .01$) (Table 3). The water intake and urine volumes were significantly higher, and body weight and DBP were significantly lower after TVL treatment (all $P < .001$) (Table 4).

Notably, dyspnea significantly improved in 71 of 73 patients, and lower limb edema disappeared in 42 of 53 patients after TLV treatment. Finally, no obvious adverse reactions occurred during the TLV treatment period.

4. Discussion

In recent decades, the prognosis of patients with PH has significantly improved because of the considerable progress in targeted drugs.^[11,12] PH-induced RHF is a crucial prognostic factor and the leading cause of death in patients with PAH.^[11,13,14] There have been no treatment breakthroughs, but TLV has become a clinically effective treatment option in recent years for patients with PH-induced RHF.

This retrospective analysis found that the TBIL, DBIL, NT-proBNP, and serum UA levels were significantly lower after the TLV treatment. Additionally, the patient's water intake and urine volumes were significantly higher, and body weight, DBP and mean arterial pressure were significantly lower after treatment. Moreover, dyspnea and lower limb edemas significantly improved after TVL treatment. These results suggest that routine therapies with TLV may be more effective than those without TLV in patients with PH.

We also found a significantly higher serum potassium concentration after TLV treatment; the serum sodium concentration also increased but not significantly. Therefore, monitoring the patient's electrolyte concentrations is necessary during TLV treatment to prevent adverse reactions.

Pro-BNP is a pro-hormone primarily secreted by the ventricle and cleaved into NT-proBNP and active BNP. NT-proBNP has more clinical applications than active BNP owing to its longer half-life and better stability.^[15] The European Society of Cardiology/European Respiratory Society guidelines recommend using NT-proBNP as part of a multiparametric assessment for prognostic and treatment goals for patients with PAH.^[1] In our study, the NT-proBNP level was significantly lower after TLV treatment, indicating that TLV may benefit RHF caused by PH.

UA is an end product of purine metabolism generated from xanthine by xanthine oxidoreductase and primarily excreted by the kidneys.^[16] Some studies have reported an elevated UA level in hypoxic states, such as chronic heart failure and PH.^[17–19] Furthermore, serum UA is a prognostic factor for adverse

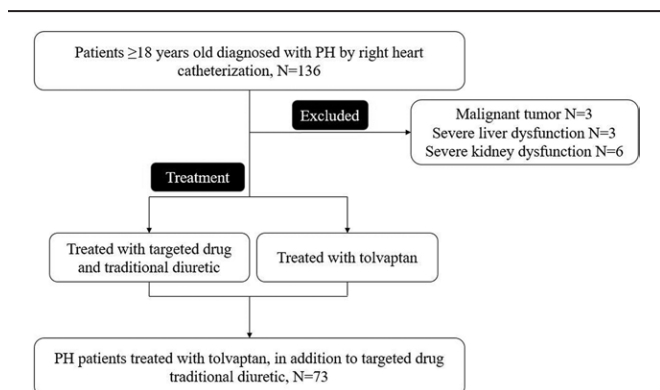


Figure 1. The flow diagram of the retrospective analysis. PH = pulmonary hypertension.

Table 1
Baseline characteristics of the studied patients.

Patient characteristics (n = 73)	Results
Age stratified, n (%)	
>65	23 (31.51%)
≤65	50 (68.49%)
Age, mean ± SD	54.29 ± 15.68
Age range	22–83
Sex, n (%)	
Female	50 (68.49%)
Male	23 (31.51%)
BMI (kg/m ²)	21.28 ± 0.49
Alcohol drinking, n (%)	3 (4.11%)
Smoking, n (%)	7 (9.59%)
mPAP range (mm Hg)	27–108
clinical classification of PH, n (%)	
PAH	35 (47.95%)
PH due to left heart disease	4 (5.48%)
PH due to lung disease and/or hypoxia	9 (12.33%)
PH due to pulmonary artery obstructions	7 (9.59%)
PH with unclear and/or multifactorial mechanisms	18 (24.66%)
WHO-FC III/IV, n (%)	67 (91.78%)

BMI = body mass index, mPAP = mean pulmonary artery pressure, PAH = pulmonary arterial hypertension, PH = pulmonary hypertension, SD = standard deviation, WHO-FC = World Health Organization functional class.

outcomes and is associated with a higher 5-year mortality rate in patients with PH.^[20–22] Some studies have demonstrated that TLV increases the serum UA level by decreasing its renal clearance.^[23] Furthermore, water intake increased in these studies, which effectively reduced urinary UA supersaturation.^[24]

However, our results demonstrated that adding TLV to targeted drug and traditional diuretic therapies decreased the serum UA level, perhaps because the patients' water intake increased. Therefore, our study suggests that TLV may improve the prognosis and reduce the 5-year mortality rate for patients with PH.

Bilirubin is a metabolic end-product of heme degradation and an important endogenous antioxidant molecule.^[25] The TBIL level is a predictive risk factor for systolic heart failure and PAH, whereas DBIL can predict PH severity and outcomes.^[26–28] We found that adding TLV to targeted drug and traditional diuretic therapies reduced the serum TBIL and DBIL levels, suggesting PH severity and prognostic improvements.

Adverse reactions have been documented with TLV, such as a rapidly increasing serum sodium level. Some have also reported liver injury after TLV administration, characterized by elevated alanine aminotransferase and bilirubin levels and an increased UA level due to reduced renal excretion.^[23,29] In terms of diuretic mechanism, TLV did not increase the serum UA and bilirubin levels, perhaps caused by a decrease in volume after TLV urination or a rapidly increasing blood sodium level. However, these mechanisms require confirmation by clinical observation.

Our study has several limitations. First, this was a single-center analysis with a small number of patients. Second, we only documented a limited number of outcome measurements to assess TLV's role in patients with PH. Third, bias may be inevitable since this was a retrospective and nonrandomized study. Hence, future follow-up studies should be multi-center analyses, include more patients, and analyze more outcome measurements to fully elucidate the role of TLV in patients with PH.

Table 2
Comparison of clinical characteristics before and after tolvaptan treatment.

Parameters	Before tolvaptan treatment	After tolvaptan treatment	t value	P value
Hb (g/dL)	13.88 ± 16.32	12.00 ± 4.06	1.164	.249
ALT (IU/L)	19.74 ± 2.79	20.87 ± 1.76	.575	.568
AST (IU/L)	29.55 ± 4.07	26.19 ± 1.54	.905	.369
TBIL (μmol/L)	31.86 ± 3.79	24.67 ± 2.55	3.440	.001
DBIL (μmol/L)	16.34 ± 2.60	13.49 ± 1.88	2.441	.018
TBA(μmol/L)	12.25 ± 3.53	13.50 ± 3.56	.577	.567
UA (μmol/L)	526.9 ± 22.99	445.3 ± 26.18	3.803	<.0001
BUN (mmol/L)	8.93 ± 0.68	9.28 ± 0.84	.658	.513
SCr (μmol/L)	84.63 ± 4.47	89.97 ± 5.51	1.430	.158
Cystatin C (mg/L)	1.31 ± 0.07	1.43 ± 0.09	1.882	.067
NT-proBNP (pg/mL)	4396 ± 594.90	2974 ± 436.00	2.321	.023
K ⁺ (mmol/L)	4.03 ± 0.07	4.27 ± 0.06	3.229	.002
Na ⁺ (mmol/L)	140.0 ± 0.58	141.3 ± 0.57	1.840	.070
Cl ⁻ (mmol/L)	103.6 ± 0.67	103.6 ± 0.71	.019	.985
Ca ²⁺ (mmol/L)	2.27 ± 0.02	2.32 ± 0.02	1.945	.056

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, DBIL = direct bilirubin, Hb = hemoglobin, NT-proBNP = N-terminal pro-brain natriuretic peptide, Scr = serum creatinine, TBA = total bile acid, TBIL = total bilirubin, UA = uric acid.

Table 3
Comparison of heart rate and blood pressure before and after tolvaptan treatment.

Parameters	Before tolvaptan treatment	after tolvaptan treatment	t value	P value
HR (bpm)	86.86 ± 1.75	86.74 ± 1.64	.059	.953
SBP (mm Hg)	109.2 ± 1.94	106.0 ± 1.64	1.843	.070
DBP (mm Hg)	68.29 ± 1.35	64.15 ± 1.20	3.502	.0008
MAP (mm Hg)	81.94 ± 1.33	78.12 ± 1.19	3.329	.001

DBP = diastolic blood pressure, HR = heart rate, MAP = mean arterial pressure, SBP = systolic blood pressure.

Table 4**Comparison of water intake, urine volume, body weight before and after tolvaptan treatment.**

Parameters	Before tolvaptan treatment	After tolvaptan treatment	t value	P value
Water intake (mL)	1044 ± 67.91	1634 ± 60.76	6.986	<.0001
Urine volume (mL)	1271 ± 100.60	1961 ± 99.50	5.633	<.0001
Body weight (kg)	57.94 ± 1.70	54.68 ± 1.59	5.731	<.0001

5. Conclusions

Adding TLV to targeted drug and traditional diuretic therapies has promising effectiveness for treating PH.

Author contributions

Qiaoli Chen conceived this study. Qiaoli Chen and Heng Luo collected and analyzed data. Qiaoli Chen wrote the manuscript. Yuping Li supervised this work. All authors have read and approved the final manuscript.

Data curation: Qiaoli Chen, Heng Luo.

Project administration: Yuping Li.

Supervision: Yuping Li.

Writing – original draft: Qiaoli Chen.

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