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ORIGINAL ARTICLE

Efficacy and safety of oral tolvaptan in patients undergoing hemodialysis: a Phase 2, double-blind, randomized, placebo-controlled trial

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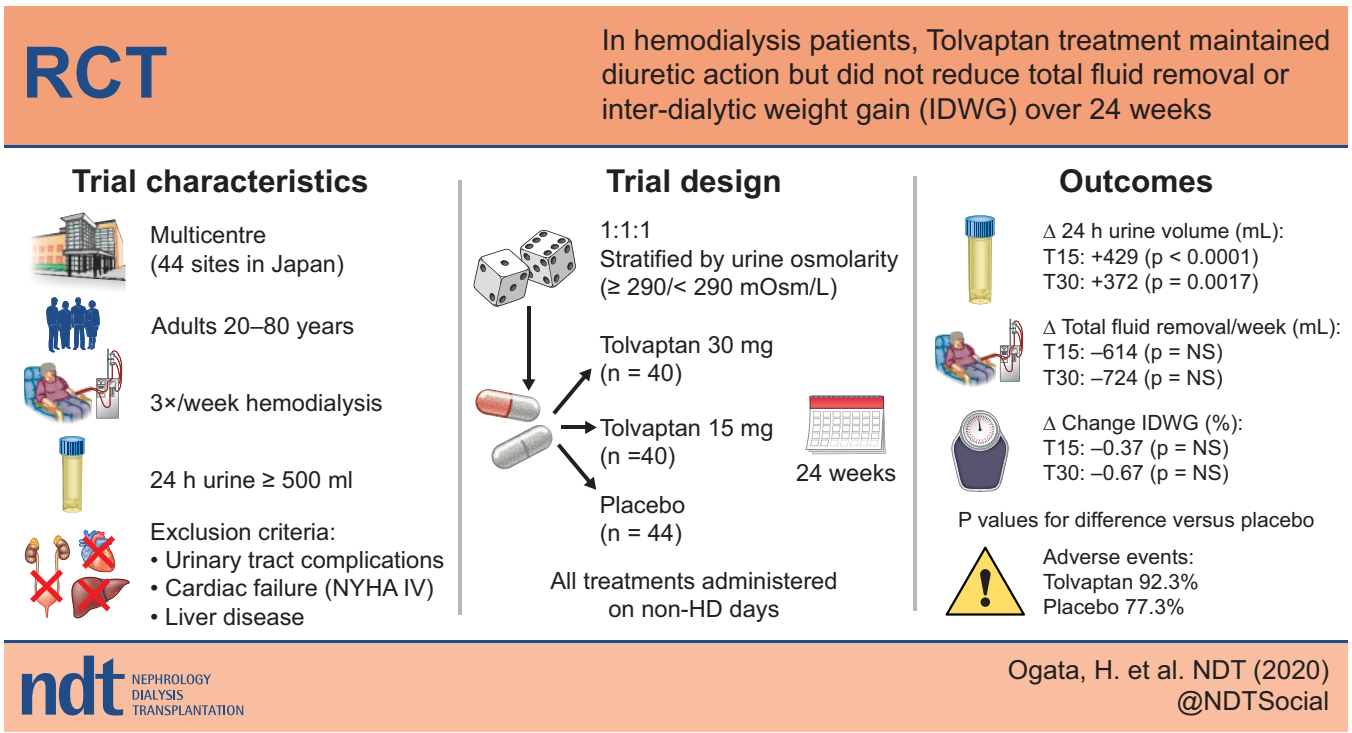
GRAPHICAL ABSTRACT



ABSTRACT

Background. Loop diuretics are used to manage fluid retention in patients with end-stage kidney disease undergoing hemodialysis (HD). This randomized, double-blind, placebo-controlled, Phase 2 trial evaluated the efficacy and safety of tolvaptan, a vasopressin V_2 receptor antagonist, in Japanese HD patients.

Methods. A total of 124 patients (24-h urine volume ≥500 mL) on thrice-weekly HD were randomized to receive oral tolvaptan 15 mg/day ($n = 40$), tolvaptan 30 mg/day ($n = 40$) or placebo ($n = 44$) for 24 weeks. Efficacy endpoints were change from baseline in 24-h urine volume, total fluid removal by HD per week and interdialytic weight gain (IDWG). Safety was assessed

KEY LEARNING POINTS

What is already known about this subject?

- the efficacy of loop diuretics, which are frequently used to control fluid retention in patients undergoing hemodialysis (HD), is reportedly insufficient in patients with advanced kidney disease and toxicity concerns limit their use at high doses;
- an unmet need exists for new agents to effectively manage fluid retention in patients undergoing HD who are refractory to conventional diuretics; and
- treatment with tolvaptan, an oral aquaretic agent that selectively antagonizes arginine vasopressin V_2 receptors and increases free water excretion by inhibiting water reabsorption in the collecting duct, has demonstrated efficacy in increasing urine volume in patients with fluid retention in heart failure and hepatic cirrhosis.

What this study adds?

- tolvaptan is well-tolerated and has the potential to sustain diuresis and preserve urine output in patients undergoing HD, although it remains unclear if tolvaptan impacts total fluid removal by HD and interdialytic weight gain; and
- the differences in mode and site of action and route of delivery between tolvaptan and loop diuretics potentially enable tolvaptan to exhibit its aquaretic action even in patients with reduced kidney function or electrolyte abnormality.

What impact this may have on practice or policy?

- tolvaptan could be a potential therapy to mitigate fluid retention in patients undergoing HD who are refractory to conventional diuretics; and
- further studies are warranted to validate the role of tolvaptan in improving clinical outcomes, such as deterioration of residual kidney function and cardiovascular mortality in HD patients.

via the incidence of treatment-emergent adverse events (TEAEs).

Results. At treatment end, the difference (95% confidence interval) from the placebo group in the mean change from baseline in 24-h urine volume was significant in the tolvaptan 15 mg {429.1 mL [95% confidence interval (CI) 231.0, 627.2]; $P < 0.0001$} and 30 mg [371.6 mL (95% CI 144.1, 599.2); $P = 0.0017$] groups. The mean changes from baseline in total fluid removal by HD and IDWG were not significantly different in the tolvaptan groups versus the placebo group. Although the proportion of patients with TEAEs was lower in the placebo group (77.3%) than in the tolvaptan groups (92.3%), tolvaptan was safe and well-tolerated during the study period.

Conclusions. Tolvaptan significantly sustained diuretic action for 24 weeks in HD patients but did not reduce total fluid removal by HD per week and IDWG to the same extent.

Keywords: aquaretic, diuretic, end-stage kidney disease, hemodialysis, tolvaptan

INTRODUCTION

In patients with end-stage kidney disease (ESKD), decreased kidney function causes fluid retention and increased blood pressure (BP) and contributes to end-organ damage. Although hemodialysis [HD; including hemodiafiltration (HDF)] effectively improves uremia and fluid retention in ESKD patients, intermittent rapid fluid removal and associated intradialytic hypotension are hypothesized to cause further renal injury and accelerate the loss of residual kidney function (RKF). This, in turn, results in decreased urine volume and increased fluid overload [1, 2], thus increasing the need for rapid fluid removal during dialysis. Diuretics are frequently used to control fluid retention in ESKD patients undergoing HD [3]. However, the efficacy of loop diuretics has been reported to be insufficient in patients with advanced kidney disease [4–6] and toxicity concerns limit their use at high doses [5]. Thus an unmet need exists for new agents to effectively manage fluid retention in HD patients refractory to conventional diuretics.

Unlike loop diuretics, tolvaptan (Otsuka Pharmaceutical, Tokyo, Japan), an oral aquaretic agent, selectively antagonizes arginine vasopressin V_2 receptors and increases free water excretion by inhibiting water reabsorption in the collecting duct [7]. Tolvaptan is currently approved for hyponatremia in heart failure and the syndrome of inappropriate secretion of antidiuretic hormone in the USA and 45 other countries [8] and for volume overload in heart failure or hepatic cirrhosis in patients who are refractory to diuretics in Japan and some Asian countries [9, 10]. In addition, tolvaptan has recently become clinically available for the treatment of autosomal dominant polycystic kidney disease (ADPKD) in Japan, the European Union, the USA and other countries [11–13]. A pilot study revealed that tolvaptan increased urine volume in patients with kidney failure on peritoneal dialysis [14]; however, the efficacy of tolvaptan in HD patients remains to be investigated and it is not yet approved for use in kidney failure.

Based on the hypothesis that tolvaptan could be expected to induce diuresis even in HD patients, we conducted a randomized controlled trial to assess the efficacy and safety of tolvaptan in this population.

MATERIALS AND METHODS

Objectives

To investigate the long-term sustainability of tolvaptan in increasing 24-h urine volume and controlling fluid removal by HD and interdialytic weight gain (IDWG), tolvaptan or placebo was administered for 24 weeks to patients undergoing HD. Additional objectives included the evaluation of safety and the exploratory efficacy outcomes of treatment with tolvaptan.

Study design

This multicenter, randomized, double-blind, placebo-controlled, parallel-group, 24-week, Phase 2 trial was conducted at 44 sites in Japan from 22 January 2015 to 30 May 2016. The trial comprised screening (1–14 days), pretreatment observation (28 days), treatment (24 weeks) and posttreatment observation (3–17 days after Day 7 assessments of Week 24 of the treatment period) periods (Supplementary data, Figure S1). The trial was conducted in accordance with the Declaration of Helsinki, the Pharmaceutical Affairs Law and the Ordinance on Good Clinical Practice and was approved by the institutional review board at each study site. Written informed consent was obtained from all patients before screening. The trial is registered at ClinicalTrials.gov (NCT02331680).

Patients

Major inclusion criteria were thrice-weekly HD/HDF, 24-h urine volume ≥500 mL/day and age 20–80 years inclusive. Key exclusion criteria were urinary tract complications due to stenosis, urolithiasis, tumor or other causes; cardiac failure (New York Heart Association Class IV) and liver disorders, such as chronic hepatitis or drug-induced liver injury. Further details are presented in the Supplementary data, Table S1.

Treatment

Eligible patients were randomized in a 1:1:1 ratio to receive tolvaptan 15 or 30 mg/day or placebo for 24 weeks on off-dialysis days. To minimize bias, treatment allocation was stratified by urine osmolarity (≥290/<290 mOsm/L) before HD in the pretreatment observation period. An independent treatment allocation manager prepared a master random allocation table using SAS 9.2 (SAS Institute Japan, Tokyo, Japan) and coded the study drug as per the operating procedures of randomization. The allocation table was sealed by the treatment allocation manager immediately after completion of treatment randomization and was kept under strict control until unblinding. The investigators, patients and trial staff were blinded to treatment randomization.

Tablets of tolvaptan (15/30 mg) or placebo, indistinguishable from each other, were administered once daily after breakfast on off-dialysis days for 24 weeks. To prevent rapid diuresis, patients in the tolvaptan 30 mg group were initiated on a once-daily dose (on off-dialysis days) of 15 mg for the first week followed by 30 mg once daily for 23 weeks. Any drug or food having potent inhibition or induction of cytochrome P450 3A4 (CYP3A4) was prohibited during the study period because CYP3A4 metabolizes tolvaptan. Initiation of any other diuretics or blood purification therapies during the study was not permitted and patients taking diuretics before enrollment were maintained on the same dose and regimen throughout the study period or until study withdrawal.

Endpoints

Efficacy. The main efficacy endpoints were changes from baseline in 24-h urine volume, total fluid removal by HD per week and IDWG. Exploratory efficacy endpoints (Supplementary data, Table S2) included dry weight (target body weight) by HD, frequency of medical treatment for muscle cramps, frequency of medical treatment for a decrease in BP during HD, number of times systolic BP dropped by ≥20 mmHg or by ≥30 mmHg during HD, lowest systolic and diastolic BP during HD, degree of postdialysis malaise and quality of life (QoL)-related outcomes, including the Kidney Disease QoL Short Form (KDQoL-SF, version 1.3) with ESKD-targeted areas and 36-item health survey and psychological burden due to fluid intake restriction.

Patients underwent thrice-weekly HD on Days 3, 5 and 7. The 24-h urine volume was measured immediately after complete urination following breakfast starting on Day 1 to the same time on Day 2 during the pretreatment period and treatment period (before study drug administration). Total fluid removal by HD per week was calculated as the total volume of fluid removed by thrice-weekly HD; if the extracorporeal ultrafiltration method was performed on the day of dialysis, the fluid removed using this method was also included. IDWG was calculated as the difference between the body weight at the previous postdialysis time point and that at each predialysis time point and expressed as a percentage change relative to the previous postdialysis body weight. For IDWG measurement, care was taken to minimize differences in clothing and patients were encouraged to urinate and defecate prior to measurement.

The 24-h urine volume, total fluid removed by HD per week and IDWG were assessed at Week 4 during the pretreatment period (baseline) and on Weeks 2, 4, 8, 12, 16, 20 and 24 during the treatment period.

Safety. Safety was assessed via the incidence of treatment-emergent adverse events (TEAEs), laboratory tests (Supplementary data, Table S3), vital signs and a 12-lead electrocardiogram (ECG).

Statistical analysis

After unblinding, the data were used for the analysis. The efficacy analysis set included all patients with available efficacy data who received one dose of the study drug. The safety analysis set included all patients who received one dose of the study drug. Because this was an exploratory trial, the sample size was not statistically estimated. However, the number of patients for enrollment was set based on the feasibility of the trial and the availability of statistical analysis for the data. Subgroup analysis was performed for the change in 24-h urine volume from baseline over 24 weeks by concomitant use of diuretics, urine osmolarity, underlying disease, complicating diabetes, daily urine volume at the introduction of HD or pretreatment observation period, HD history and psychological burden due to fluid restriction as stratification factors. The change from baseline to the end-of-study assessment in main efficacy endpoints was compared between the placebo group and each tolvaptan group using the unpaired/Student's *t*-test. The point estimates of the differences in each of these comparisons and their 95% confidence intervals (CIs) were calculated. Multiplicity adjustment was not performed because of the exploratory design of this trial. For the analysis of the efficacy variables at the end-of-study assessment, missing values were imputed using the last

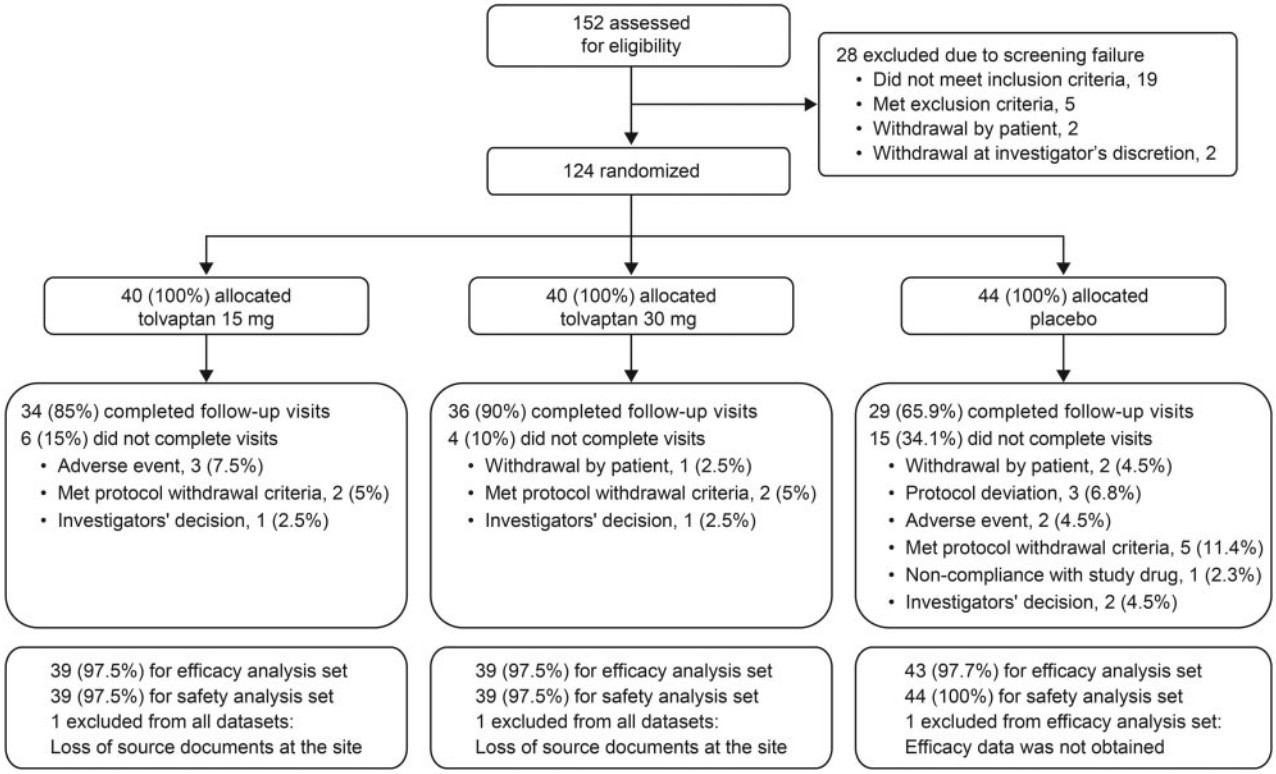


FIGURE 1: Patient disposition.

observation carried forward (LOCF) method. Mixed-model analyses for the change from baseline at each time point were also conducted using the compound symmetry covariance structure for the main efficacy endpoints. Furthermore, *post hoc* analyses were performed—two sensitivity analyses for missing data at the end-of-study assessment for main efficacy endpoints using baseline value and multiple imputation methods and interaction analyses between the change in 24-h urine volume from baseline at the end-of-study assessment by stratification factors and treatment groups (combined tolvaptan versus placebo). The significance level was 5% (two-sided). Analyses were performed using SAS 9.3 (SAS Institute Japan, Tokyo, Japan).

RESULTS

Patient disposition and baseline characteristics

Of the 152 patients screened, 124 were randomly assigned to the three groups: tolvaptan 15 mg/day ($n = 40$), tolvaptan 30 mg/day ($n = 40$) or placebo ($n = 44$) (Figure 1). Ninety-nine patients completed and 25 patients discontinued the trial, with more patients discontinuing in the placebo group [15/44 (34.1%)] than in the tolvaptan groups [10/80 (12.5%)]. The most frequent reason for discontinuation was adverse events [3/40 (7.5%)] in the tolvaptan 15 mg group and met protocol withdrawal criteria in the tolvaptan 30 mg [2/40 (5.0%)] and placebo [5/44 (11.4%)] groups (Figure 1). One patient in each tolvaptan group was excluded from all data sets because of the loss of source documents at the site, and one patient in the placebo group was excluded from the efficacy analysis set because of unavailability of efficacy data. Demographics and baseline characteristics were generally similar across treatment groups (Table 1). Baseline concomitant use of diuretics was consistent across groups.

Efficacy outcomes

24-h urine volume. The 24-h urine volume in the placebo group showed a consistent decrease from baseline at all time points assessed (Figure 2a). In contrast, 24-h urine volume in both the tolvaptan groups increased from Week 2 and was consistently higher versus the placebo group through the treatment period (Figure 2a), with a significant difference from placebo in the mean change from baseline [tolvaptan 15 mg: 429.1 mL (95% CI 231.0–627.2); $P < 0.0001$ and tolvaptan 30 mg: 371.6 mL (95% CI 144.1–599.2); $P = 0.0017$] at end of treatment (Table 2). On subgroup analysis, 24-h urine volume in the placebo group decreased regardless of the concomitant use of loop diuretics, while the diuretic effect of tolvaptan was confirmed in patients in both the subgroups (Supplementary data, Figure S2 and Table S4). Although no obvious difference in the effect of tolvaptan was confirmed using other stratification factors (Supplementary data, Tables S5–S8 and Tables S10–S11), the interaction analysis between daily urine volume in the pretreatment observation period and treatment group was significant ($P = 0.0018$) (Supplementary data, Table S9) and the increase in 24-h urine volume was higher among patients in the higher pretreatment daily urine volume category than in the tolvaptan group. The increase in 24-h urine volume by tolvaptan was also-confirmed by mixed-model analysis (Supplementary data, Table

Table 1. Demographics and patient baseline characteristics (safety analysis set)

Characteristics	Tolvaptan 15 mg group ($n = 39$)	Tolvaptan 30 mg group ($n = 39$)	Placebo group ($n = 44$)
Gender (male)	35 (89.7)	28 (71.8)	40 (90.9)
Age (years), mean ± SD	64.2 ± 11.0	60.5 ± 12.6	64.4 ± 8.7
Height (cm), mean ± SD	164.46 ± 6.46	163.69 ± 9.51	163.64 ± 7.12
Dry weight (kg)[a], mean ± SD	63.40 ± 10.42	64.24 ± 13.38	61.15 ± 11.12
Underlying disease			
Diabetic nephropathy	18 (46.2)	20 (51.3)	24 (54.5)
Chronic glomerulonephritis	9 (23.1)	9 (23.1)	8 (18.2)
Nephrosclerosis	6 (15.4)	6 (15.4)	4 (9.1)
Polycystic kidney	3 (7.7)	3 (7.7)	3 (6.8)
Other	4 (10.3)	2 (5.1)	6 (13.6)
HD history (months), mean ± SD	17.8 ± 17.3	18.4 ± 21.5	16.0 ± 20.3
Type of dialysis			
HD	33 (84.6)	37 (94.9)	40 (90.9)
Hemodiafiltration	6 (15.4)	2 (5.1)	4 (9.1)
Duration (h/time)[b], mean ± SD	3.63 ± 0.54	3.75 ± 0.45	3.81 ± 0.40
Concomitant use of diuretics			
Loop diuretics alone	18 (46.2)	16 (41.0)	19 (43.2)
Thiazide diuretics alone	0 (0.0)	0 (0.0)	1 (2.3)
Loop diuretics + thiazide diuretics	1 (2.6)	2 (5.1)	5 (11.4)
None	20 (51.3)	21 (53.8)	19 (43.2)
Dose of loop diuretics			
Furosemide-equivalent dose (mg/day)[c], median (minimum, maximum)	40.0 (10, 240)	40.0 (40, 120)	40.0 (20, 240)
24-h urine volume (mL)[d, e], mean ± SD	1015.4 ± 470.5	895.3 ± 361.1	960.3 ± 442.3
Total volume of fluid removal by HD per week (mL)[d, f], mean ± SD	5392.8 ± 3123.8	5596.4 ± 3240.8	5499.8 ± 2562.1
IDWG, 2-day interval (%)[d, g], mean ± SD	3.02 ± 2.06	3.32 ± 2.11	3.54 ± 1.64

Data are *n* (%), unless otherwise indicated.
[a]Patient numbers: tolvaptan 15 mg, $n = 38$; tolvaptan 30 mg, $n = 39$ and placebo, $n = 42$. Data from three patients (one and two in the tolvaptan 15 mg and placebo groups, respectively) were not included because of missing data in the pretreatment observation period.
[b]Duration (h/time): frequency of dialysis was fixed at three times/week in the protocol.
[c]Sixty milligrams of azosemide and 8 mg of torasemide were calculated to be equivalent to 40 mg of furosemide.
[d]Data are for patients included in the efficacy analysis set.
[e]Patient numbers: tolvaptan 15 mg, $n = 38$; tolvaptan 30 mg, $n = 38$ and placebo, $n = 42$.
[f]Patient numbers: tolvaptan 15 mg, $n = 39$; tolvaptan 30 mg, $n = 39$ and placebo, $n = 43$.
[g]Patient numbers: tolvaptan 15 mg, $n = 39$; tolvaptan 30 mg, $n = 39$ and placebo, $n = 43$.

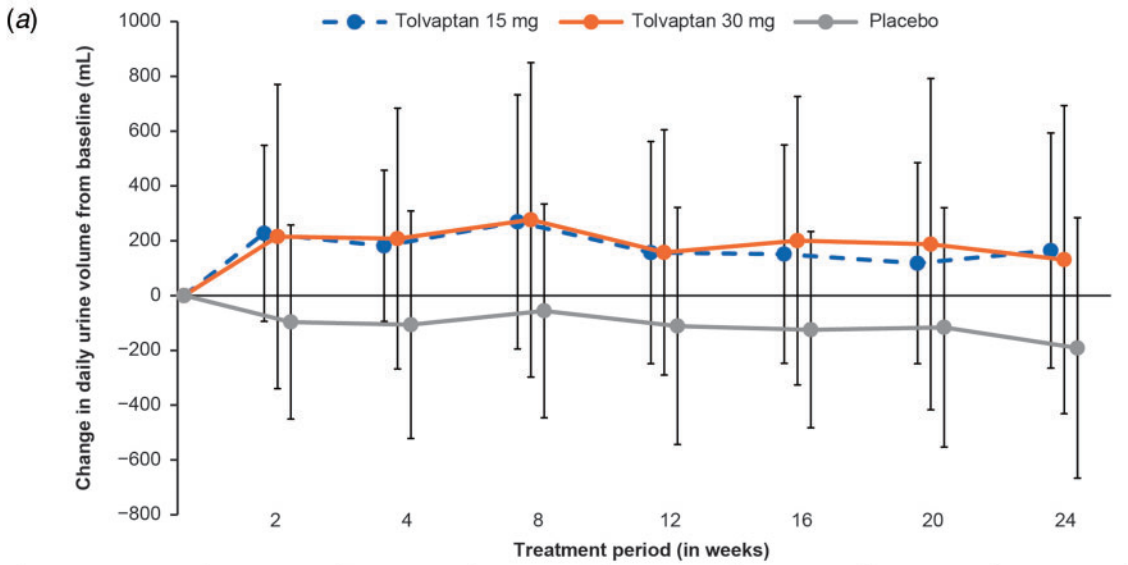
S12). The results of *post hoc* analysis for 24-h urine volume by baseline value and multiple imputation methods were similar to those by the LOCF method (Supplementary data, Tables S15 and S16).

Total fluid removal by HD per week. From Weeks 8 to 24, the weekly total fluid removal by HD continuously increased in the placebo group, while it plateaued in the tolvaptan groups (Figure 2b). At the end of treatment, the mean change from baseline was not significantly different in the tolvaptan groups versus the placebo group [tolvaptan 15 mg: −613.6 mL (95% CI −1527.4–300.1); P = 0.1852 and tolvaptan 30 mg: −724.2 mL (95% CI −1588.6–140.3); P = 0.0994] (Table 2). The results from the mixed-model analysis are presented in the Supplementary data, Table S13. The results of *post hoc* analysis for the weekly total fluid removal by HD by baseline value and multiple imputation methods were similar to those by the LOCF method (Supplementary data, Tables S15 and S16).

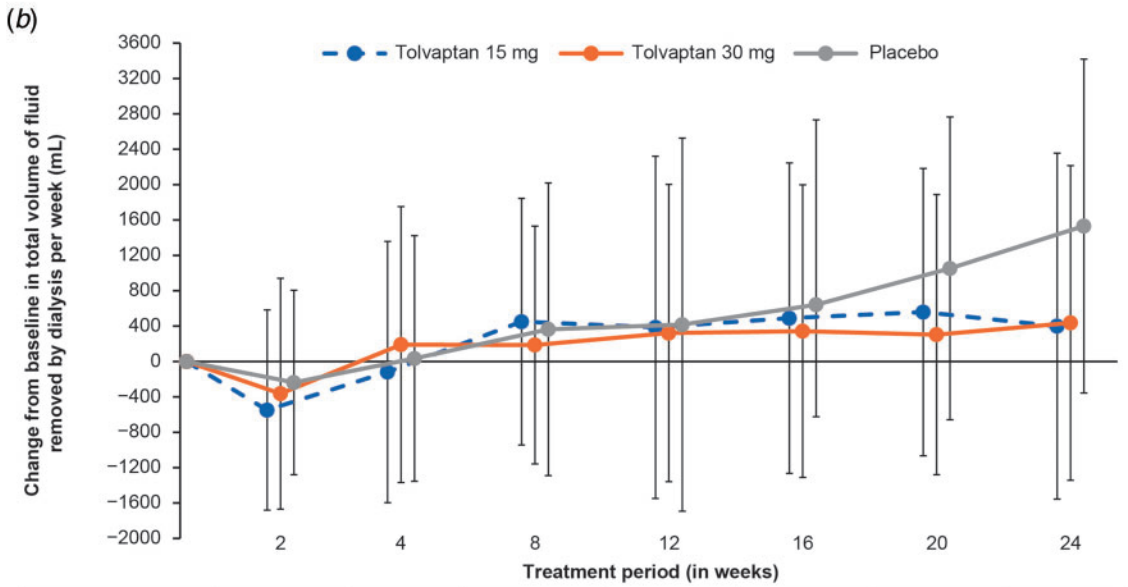
Interdialytic weight gain. At the end of treatment, the mean change from baseline in IDWG (2-day interval) was not significantly different in the tolvaptan groups versus the placebo group [tolvaptan 15 mg: −0.37% (95% CI −1.19–0.45); P = 0.3720 and tolvaptan 30 mg: −0.67% (−1.45–0.11); P = 0.0927] (Table 2). The Supplementary data, Table S14 presents the results from the mixed-model analysis. The results of *post hoc* analysis for IDWG by baseline value and multiple imputation methods were similar to those by the LOCF method (Supplementary data, Tables S15 and S16).

Other outcomes. A favorable trend toward a lower frequency of medical treatment for muscle cramps was observed in patients who received tolvaptan versus placebo (Supplementary data, Figure S3).

No notable differences were observed between the placebo and tolvaptan groups in achievement of dry weight by HD (Supplementary data, Table S17); frequency of medical treatment for a decrease in BP (Supplementary data, Tables S18 and S19); lowest systolic and diastolic BP (Supplementary data, Table S20); number of times systolic BP decreased by ≥20 or ≥30 mmHg during HD (Supplementary data, Tables S21 and S22); psychological burden due to fluid intake restriction (Supplementary data, Table S23); KDQoL-SF overall score, including ESKD-targeted areas (Supplementary data, Table S24), 36-item health survey (Supplementary data, Table S25) and Question 2 or 22 (Supplementary data, Table S26) and degree of malaise after HD (Supplementary data, Tables S27–S29).



Week	2	4	8	12	16	20	24
Tolvaptan 15 mg, n	36	37	37	37	35	34	33
Tolvaptan 30 mg, n	37	37	38	38	36	34	35
Placebo, n	42	41	37	37	34	30	29



Week	2	4	8	12	16	20	24
Tolvaptan 15 mg, n	39	38	38	38	36	34	33
Tolvaptan 30 mg, n	39	39	39	37	37	36	36
Placebo, n	43	42	40	38	36	31	30

FIGURE 2: (**a**) Mean ± SD change in 24-h urine volume from baseline to each time point during the treatment period (efficacy population) and (**b**) weekly fluid removal during HD. Only patients with both nonmissing baseline values and nonmissing values at each time point were included in the analysis.

Safety

Overall 100, 114 and 113 TEAEs were observed in 87.2% (34/39), 97.4% (38/39) and 77.3% (34/44) of patients in the tolvaptan 15 mg, tolvaptan 30 mg and placebo groups, respectively. The most frequently observed TEAEs in any treatment group were nasopharyngitis, diarrhea, vomiting, contusion and thirst (Table 3). Serious TEAEs were observed in 6 (15.4%), 7 (17.9%) and 10 (22.7%) patients in the tolvaptan 15 mg, tolvaptan 30 mg and placebo groups, respectively (Supplementary data, Table S30). TEAEs leading to discontinuation were reported in 4 (10.3%), 0 (0%) and 3 (6.8%) patients in the tolvaptan 15 mg, tolvaptan 30 mg and placebo groups, respectively.

Table 2. Change in main efficacy end points from baseline to end of study (efficacy analysis set)

End points	n[a]	Change from baseline		
			Difference from placebo group	
		Mean ± SD	Point estimate (95% CI)	t-test P-value
Treatment group				
24-h urine volume (mL)				
Tolvaptan 15 mg	38	169.2 ± 422.2	429.1 (231.0–627.2)	<0.0001
Tolvaptan 30 mg	38	111.8 ± 557.7	371.6 (144.1–599.2)	0.0017
Placebo	42	−259.9 ± 463.8		
Total volume of fluid removal by HD per week (mL)				
Tolvaptan 15 mg	39	485.9 ± 1979.3	−613.6 (−1527.4–300.1)	0.1852
Tolvaptan 30 mg	39	375.4 ± 1721.8	−724.2 (−1588.6–140.3)	0.0994
Placebo	43	1099.5 ± 2160.5		
IDWG, 2-day interval (%)				
Tolvaptan 15 mg	39	0.38 ± 1.80	−0.37 (−1.19–0.45)	0.3720
Tolvaptan 30 mg	39	0.08 ± 1.62	−0.67 (−1.45–0.11)	0.0927
Placebo	43	0.75 ± 1.91		

[a]Number of patients with both nonmissing values at baseline and at the end of the treatment period.
Patient numbers with complete data: 24-h urine volume: tolvaptan 15 mg, $n = 33$; tolvaptan 30 mg, $n = 35$ and placebo, $n = 29$; total volume of fluid removal: tolvaptan 15 mg, $n = 33$; tolvaptan 30 mg, $n = 36$ and placebo, $n = 30$ and IDWG: tolvaptan 15 mg, $n = 33$; tolvaptan 30 mg, $n = 36$ and placebo, $n = 30$.

Table 3. Incidence of TEAEs occurring in ≥5% of patients in any treatment group (safety analysis set)

TEAEs	Tolvaptan			Placebo ($n = 44$), n (%)
	15 mg ($n = 39$), n (%)	30 mg ($n = 39$), n (%)	Total ($n = 78$), n (%)	
Total number of patients with TEAEs	34 (87.2)	38 (97.4)	72 (92.3)	34 (77.3)
Infections and infestations				
Nasopharyngitis	9 (23.1)	14 (35.9)	23 (29.5)	10 (22.7)
Folliculitis	0 (0.0)	2 (5.1)	2 (2.6)	0 (0.0)
Injury, poisoning and procedural complications				
Contusion	1 (2.6)	7 (17.9)	8 (10.3)	3 (6.8)
Shunt stenosis	0 (0.0)	2 (5.1)	2 (2.6)	4 (9.1)
Wound	2 (5.1)	0 (0.0)	2 (2.6)	3 (6.8)
Gastrointestinal disorders				
Diarrhea	1 (2.6)	5 (12.8)	6 (7.7)	4 (9.1)
Vomiting	2 (5.1)	4 (10.3)	6 (7.7)	1 (2.3)
Investigations				
Blood potassium increased	2 (5.1)	0 (0.0)	2 (2.6)	4 (9.1)
BP decreased	3 (7.7)	1 (2.6)	4 (5.1)	2 (4.5)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	3 (7.7)	0 (0.0)	3 (3.8)	1 (2.3)
Skin and subcutaneous tissue disorders				
Eczema	0 (0.0)	2 (5.1)	2 (2.6)	3 (6.8)
Miliaria	0 (0.0)	2 (5.1)	2 (2.6)	0 (0.0)
General disorders and administration site conditions				
Thirst	4 (10.3)	3 (7.7)	7 (9.0)	1 (2.3)
Cardiac disorders				
Angina pectoris	2 (5.1)	0 (0.0)	2 (2.6)	1 (2.3)
Nervous system disorders				
Headache	2 (5.1)	1 (2.6)	3 (3.8)	0 (0.0)
Metabolism and nutrition disorders				
Hypoglycemia	0 (0.0)	2 (5.1)	2 (2.6)	0 (0.0)
Vascular disorders				
Hypertension	2 (5.1)	0 (0.0)	2 (2.6)	0 (0.0)
Blood and lymphatic system disorders				
Iron deficiency anemia	2 (5.1)	0 (0.0)	2 (2.6)	1 (2.3)
Psychiatric disorders				
Insomnia	2 (5.1)	0 (0.0)	2 (2.6)	0 (0.0)

TEAEs were coded from the Medical Dictionary for Regulatory Activities version 19.0.

TEAEs potentially related to the study drug were observed in 8 (20.5%), 7 (17.9%) and 4 (9.1%) patients in the tolvaptan 15 mg, tolvaptan 30 mg and placebo groups, respectively (Supplementary data, Table S31).

One (2.6%) patient in the tolvaptan 15 mg group reported elevated alanine aminotransferase and aspartate aminotransferase (peak levels 70 and 50 U/L, respectively), which resolved without cessation of the study drug. No obvious changes in serum sodium (Supplementary data, Figure S4), creatinine and osmolarity, blood urea nitrogen (Supplementary data, Table S32) and other clinical laboratory tests were observed among the treatment groups. No clinically relevant findings on ECG (Supplementary data, Table S33) and vital signs (Supplementary data, Tables S34 and S35) were reported. During pre- and postdialysis measurement of vital signs, no obvious changes in BP were observed in any treatment group throughout the treatment period. No deaths were reported during the trial.

DISCUSSION

The mode and site of action and route of delivery between tolvaptan and loop diuretics differ in several ways. First, since the predominant effect of loop diuretics is to inhibit the sodium (Na^+)–potassium (K^+)–chloride ($2Cl^-$) cotransporter at the apical membrane of the thick ascending limb of Henle, the loop diuretics must be secreted into the lumen of the urinary tract at the proximal tubules [15, 16]. In patients with kidney failure, impaired renal tubular function may decrease the secretion of loop diuretics into the tubular lumen, causing an insufficient delivery of loop diuretics. Furthermore, reduced renal blood flow in the ascending limb of the medulla may cause renal ischemia, leading to inefficient Na^+ reabsorption [17, 18]. Therefore an impaired loop of Henle in the medulla combined with insufficient loop diuretic delivery could be responsible for resistance to loop diuretics in ESKD patients [5, 15, 19]. In contrast, tolvaptan antagonizes vasopressin V_2 receptors located in the basolateral membrane of the renal collecting ducts [17], indicating that tolvaptan is delivered through renal blood flow and not glomerular filtrate. Additionally, the collecting ducts are considered more resistant to ischemia and hypoxia owing to a lower oxygen requirement compared with the loop of Henle. Thus their function is relatively preserved even in ESKD patients [6]. Tolvaptan is therefore expected to work even in HD patients with severely impaired RKF, provided the renal blood flow is maintained. Second, loop diuretics are known to decrease renal blood flow [18], whereas tolvaptan increases it [17]. Since loop diuretics have a strong natriuretic action, they are likely to cause a decrease in extracellular Na^+ levels and intravascular volume, consequently activating the renin–angiotensin system (RAS) and sympathetic tone. In contrast, tolvaptan induces aquaresis without significant urinary Na^+ loss and therefore is likely to affect neither RAS nor sympathetic tone [17, 20]. Interestingly, RAS inhibition is associated with better preservation of RKF in HD patients [21]. Taken together, the differences in mode and site of action and route of delivery between tolvaptan and loop diuretics may enable tolvaptan to exhibit its aquaretic action even in patients with reduced kidney function or electrolyte abnormality. This could also explain the significantly higher change from baseline in 24-h urine volume in both the tolvaptan groups versus in the placebo group.

Of note, no significant decrease was observed in IDWG and total fluid removal by HD in the tolvaptan groups, especially in the early treatment period, in spite of significant increases in 24-h urine volume. We hypothesize that the aquaretic action of tolvaptan initially causes an increase in serum osmolarity followed by stimulation of the feeling of thirst. The resultant increase in fluid intake could have abrogated the effect of tolvaptan on IDWG and total fluid removal by HD. This hypothesis could be supported by the fact that no significant changes in serum Na^+ concentration or osmolarity were observed during the treatment period. Furthermore, the patients in this study could excrete fluid to the same extent through urine, as indicated by their 24-h urine volume of $\geq$500 mL, suggesting that tolvaptan may not have had definitive effects on total fluid removal by HD and IDWG.

Although urine output achieved by diuretics, such as natriuretics (e.g. loop diuretics) and aquaretics (tolvaptan), is different from that arising from RKF in several ways (e.g. excretion of uremic toxin), their role in adjusting fluid volume in HD patients is similar. High ultrafiltration rates in HD patients are associated with a great risk of all-cause and cardiovascular death [22], suggesting the importance of maintaining urine output in HD patients. The decrease in fluid removal by HD with diuretics is expected to mitigate a rapid change in body fluid volume. Furthermore, tolvaptan is already used effectively in Japan for fluid removal in patients with congestive heart failure (CHF) and chronic kidney disease (at the predialysis stage) [23, 24]. CHF is frequently observed in HD patients, hence tolvaptan may be clinically effective in HD patients with CHF.

Hepatic dysfunction has been reported in tolvaptan clinical trials for ADPKD [11, 13]. In this study, one patient in the tolvaptan 15 mg group reported a mild increase in alanine aminotransferase and aspartate aminotransferase. However, these TEAEs resolved during the study period. The incidence of thirst was lower and that of diarrhea was lower or comparable to that reported in previous tolvaptan clinical trials [11, 13, 25]. No clinically relevant findings were reported in vital signs, ECG and clinical laboratory tests among the groups. No deaths were reported during the trial and the incidence of serious TEAEs and TEAEs leading to the discontinuation of study drugs was similar among the groups. Overall, tolvaptan was well-tolerated during the 24-week treatment period.

This study has some limitations. First, more patients withdrew from this study in the placebo group versus the tolvaptan groups. Therefore the possibility of attrition bias cannot be excluded. Second, only patients with urine volume $\geq$500 mL/day were enrolled to include those with a substantial residual urine volume to allow for the tolvaptan action of increasing urine volume. Thus the results from this study could not confirm the effect of tolvaptan on urine volume in oliguric patients with urine volume $<$500 mL/day. Third, we are unable to discuss the diuretic action of tolvaptan in patients who are severely resistant to loop diuretics based on the results of the current study,

because the dose of the concomitantly used loop diuretics was low (furosemide-equivalent median dose 40 mg/day). Therefore it also remains unclear whether tolvaptan exhibits aquaretic action in patients who are severely resistant to loop diuretics.

This study suggests that tolvaptan is well-tolerated and increases urine volume and preserves urine output for 24 weeks in HD patients. However, it remains unclear if tolvaptan treatment results in a lower volume of fluid removal during HD and IDWG. Further studies are warranted to validate these findings and to define the role of tolvaptan more clearly in improving clinical outcomes, such as deterioration of RKF and cardiovascular mortality, in HD patients.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

H.O., T.A., N.S. and T.O. conceived and designed the trial and contributed to data acquisition. N.S. and T.O. analyzed the data. H.O., T.A., N.S., T.O. and H.N. contributed to interpretation of the data and critically revised the manuscript, read and approved the final manuscript and agreed to be accountable for all aspects of the manuscript.

CONFLICT OF INTEREST STATEMENT

H.O. reports consulting fees from Otsuka Pharmaceutical for this work; lecture fees from Kyowa Hakko Kirin, Otsuka Pharmaceutical, Ono Pharmaceutical and Torii Pharmaceuticals; consulting fees from YL Biologics and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology and Japan Society for the Promotion of Science, outside the submitted work. N.S. and T.O. are full-time employees of Otsuka Pharmaceuticals. H.N. was a full-time employee and a member of the employee stock ownership program of Otsuka Pharmaceutical until the end of 2018. T.A. reports consulting fees from Otsuka Pharmaceutical for this work; lecture fees from Chugai Pharmaceutical; consulting fees from Japan Tobacco, GlaxoSmithKline, Nipro and Sanwa Chemical; consulting and manuscript fees from Astellas Pharma and consulting and lecture fees from Bayer Yakuhin, Kissei Pharmaceutical, Ono Pharmaceutical, Fuso Pharmaceutical Industries, Torii Pharmaceutical and Kyowa Hakko Kirin outside the submitted work.

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Utility of serological tumor biomarkers for surveillance of hepatocellular carcinoma in patients undergoing dialysis

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ABSTRACT

Background. Patients undergoing dialysis are at risk of hepatocellular carcinoma (HCC) and preferably should undergo HCC surveillance. We investigated the utility of HCC tumor markers for HCC surveillance in patients undergoing dialysis.

Methods. Three serum markers specific for HCC, namely alpha-fetoprotein (AFP), *Lens culinaris* agglutinin A-reactive fraction of AFP (AFP-L3) and des-gamma-carboxy prothrombin (DCP), were measured in dialysis patients with and without a diagnosis of HCC ($n = 60$ and 507, respectively). The predictive value of each marker and that of a diagnostic score (GALAD score) based on patient age and gender as well as the same three markers were evaluated by receiver-operating characteristic (ROC) analysis, as well as sensitivity and specificity.

Results. AFP, DCP and the GALAD scores showed high predictive values for HCC, with areas under the ROC curve of >0.85. This effectiveness remained when focusing on small HCC (≤3 cm or ≤2 cm) or early-stage HCC (Stage I), as well as after propensity score matching of background characteristics of HCC and non-HCC patients. In particular, DCP and GALAD score had excellent predictive abilities for HCC.

Conclusions. Measuring serum tumor markers for HCC can serve as a complement to imaging studies in the surveillance of HCC in patients undergoing dialysis, and reduce the likelihood of advanced HCC at detection and diagnosis.

Keywords: hepatocellular carcinoma, serum tumor markers, surveillance

INTRODUCTION

Patients undergoing dialysis are at risk of hepatocellular carcinoma (HCC). The prevalence of hepatitis C virus infection, which is the major risk factor for HCC development, is reportedly higher in dialysis patients than in the general population [1–4]. Diabetes mellitus, another important risk factor for HCC [5], causes diabetic nephropathy and is therefore among the major causes of end-stage renal disease and dialysis [6]. In addition, secondary hemosiderosis of the liver due to red blood cell transfusion in dialysis patients may further increase the risk of HCC development.

It is known that surveillance for HCC in at-risk patients facilitates early tumor detection and plays a relevant role in improving the survival of patients with HCC [7–10]. Since patients requiring dialysis generally have conditions that increase their risk of HCC, surveillance is important in this population. However, it is often difficult to perform effective HCC surveillance with imaging studies in patients undergoing dialysis, which results in this population having more advanced HCC