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Review

Update of acute and long-term tolvaptan therapy

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ABSTRACT

One of the vasopressin type 2 receptor antagonists, tolvaptan, has been used to treat congestive heart failure patients for over seven years in Japan. Beyond the initially suggested standard procedure, tolvaptan is currently used in patients with acute heart failure soon after their admission or it is used for long-term treatment in the ambulatory situation. Nevertheless, definitive evidence is lacking, particularly for the implication of long-term tolvaptan therapy. Now is the time to update the accumulating evidence and consider the optimal therapeutic strategy for short- and long-term tolvaptan therapy.

Contents

Introduction

One of the vasopressin type 2 receptor antagonists, tolvaptan, has been used in the USA since 2009 with the indications of hypervolemic and euvolemic hyponatremia. In Japan, tolvaptan was approved in 2010 for the following indication: volume overload in heart failure (HF) patients refractory to other conventional diuretic therapies, irrespective of the existence of hyponatremia [1]. Owing to its unique aquauretic effect, tolvaptan has become an essential tool for the management of inpatients with congestive HF thus far, and evidence for the efficacy and safety of tolvaptan therapy has been accumulating particularly in Japan. In the short term, tolvaptan improves congestive symptoms and ameliorates hyponatremia, relatively maintaining hemodynamics, in a strictly monitored inpatient setting [2].

The initially proposed protocol is to continue tolvaptan therapy only during hospitalization. However, tolvaptan has recently been used more in various situations in real-world practice: soon after the hospitalization for acute HF or long-term ambulatory usage,

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considering the favorable clinical outcomes experienced by the clinicians [3]. Now is a time to review current accumulating evidence and update optimal therapeutic strategy in such expanded situations.

Short-term use of tolvaptan in patients with acute HF

The therapeutic goal for treatment of acute HF, including the acute worsening of chronic HF, is an immediate stabilization of hemodynamics: amelioration of organ congestion and improvement in systemic circulation. For the achievement of this goal, a diuretic is a key tool, because approximately 70% of patients with acute HF have congestive symptoms [4].

As stated in the Japanese Circulation Society guidelines for diagnosis and treatment of acute and chronic HF [5], intravenous administration of furosemide within the first 60 min is recommended for the appropriate patients, which are assigned to the clinical scenario 1 or 2, or wet and warm status in the Nohria-Stevenson criteria [6].

However, furosemide has several negative impacts: decreasing glomerular filtration ratio [7] and stimulating plasma renin activity [8]. Continuous intravenous administration of furosemide may not have an advantage in preserving renal function over the bolus administration [9].

Considering these critical limitations with furosemide, tolvaptan has recently been used in patients with acute HF soon after their hospitalizations. There are accumulating reports demonstrating the acute effect of tolvaptan. For example, Gheorghiade and colleagues initially performed a double-blinded randomized control study, in which 25-day tolvaptan therapy (30 mg, 45 mg, or 60 mg/day) increased urine volume and decreased body weight, maintaining heart rate, blood pressure, serum potassium, and renal function, compared with the placebo [10].

We have recently summarized the acute effect of tolvaptan therapy by assessing 14 randomized control studies (using a placebo in some studies and conventional diuretic therapies in others) (Table 1) [11]. As we experienced in clinical practice, tolvaptan therapy increased urine volume and ameliorated dyspnea at day 1, followed by an increase in serum sodium concentration and a reduction in body weight.

What is an optimal therapeutic strategy with tolvaptan in patients with acute HF?

Considering the results of recent studies, optimal timing of tolvaptan administration, optimal dose of tolvaptan, and optimal adjustment of other concomitant diuretics may be keys for the successful tolvaptan therapy for acute HF.

(1) Optimal timing of TLV therapy

Matsukawa and colleagues demonstrated that early tolvaptan administration within 3 days following patients' hospitalizations was associated with better response to tolvaptan (over 50% of increase in urine volume from the baseline), earlier initiation of ambulatory cardiac rehabilitation, shorter hospital stay, and lower rate of in-hospital death [12]. Early initiation of tolvaptan therapy was independently associated with shorter length of hospital stay in another study with 247 patients with acute HF [13].

Considering these studies, tolvaptan may be considered in the second 60 min when the furosemide intravenous shot is refractory in the first 60 min in patients with acute HF (class IIa and evidence level A) [5].

(2) Optimal dose of TLV

Recently two randomized control trials to investigate the acute effect of tolvaptan conducted abroad (TACTICS-HF trial [14] and SECRET trial [15]) did not demonstrate any advantages of tolvaptan in preserving renal function over the placebo group. We should emphasize that tolvaptan was administered at 30 mg/day in both trials. Our meta-analysis showed favorable outcome in preserving renal function in the tolvaptan group compared with the control group when tolvaptan was administered at 7.5–15 mg/day; whereas such an advantage in renal function disappeared when 30 mg/day of tolvaptan was administered [11].

Considering that aggressive diuresis may induce hemodynamic instability and reduction in renal blood flow [16], 3.75 mg or 7.5 mg of tolvaptan may be recommended to preserve renal function as an initial dose.

(3) Adjustment of concomitant diuretics

Hanatani and colleagues conducted a multicenter, prospective, randomized study in 44 patients with congestive HF and chronic kidney disease treated with conventional diuretics [17]. Serum creatinine concentration was significantly increased in the diuretics-fixed group but decreased in the diuretics-reduced by half group at 7–14 days.

In the TACTICS-HF trial, the dose of furosemide was fixed during the study period [14]. The dose of furosemide was variable in the

Table 1
Fourteen randomized control trials assessing the acute effect of tolvaptan [11].

Reference	Year	Location	Study design	Control	Tolvaptan		Number of patients	
					Dose (mg/day)	Dosing period (days)	Tolvaptan	Control
Gheorghiade [10]	2003	US	Double-blind	Placebo	30/45/60	25	191	63
Gheorghiade (ACTIV) [38]	2004	US, ARG	Double-blind	Placebo	30/60/90	60	239	80
Gheorghiade (EVEREST) [39]	2007	US, EUR	Double-blind	Placebo	30	7	2072	2061
Matsuzaki [40]	2011a	JPN	Double-blind	Placebo	15/30/45	7	89	28
Matsuzaki (QUEST) [41]	2011b	JPN	Double-blind	Placebo	15	7	53	57
Udelson [42]	2011	US	Double-blind	Placebo	30	7	20	21
Jujo [19]	2016	JPN	Open-label	Furosemide	7.5	5	30	30
Kimura [43]	2016	JPN	Single-blind	Furosemide	7.5–15	NA	26	26
Matsue (AQUAMARINE) [44]	2016	JPN	Open-label	Diuretics	15	2	108	109
Matsuyama [45]	2016	JPN	Open-label	Diuretics	7.5	5	25	25
Felker (TACTICS) [14]	2017	US	Double-blind	Placebo	30	0/24/48 h	129	128
Konstam (SECRET) [15]	2017	US	Double-blind	Placebo	30	7	122	128
Tamaki [46]	2017	JPN	Open-label	Diuretics	7.5–15	48 h	26	24
Inomata (K-STAR) [47]	2017	JPN	Open-label	Furosemide	≤15	7	40	41

SECRET trial, but remained unchanged at high dose (from 154 mg/day at day 0 to 141 mg/day at day 3) [15].

Loop diuretics increase plasma renin activity and aldosterone concentration [18]; whereas plasma renin activity remained unchanged during tolvaptan therapy [19]. Considering these results, the effort to reduce the dose of concomitant diuretics may be recommended for the better clinical outcome, although we should also understand that sufficient decongestion is ideal before discharge.

Long-term tolvaptan therapy

The EVEREST trial, the first prospective long-term randomized control trial, could not demonstrate the advantage of 2-year tolvaptan therapy in survival and freedom from events over the placebo [20]. Nevertheless, many HF patients receive long-term tolvaptan therapy thus far, particularly in Japan, probably considering the favorable clinical response of tolvaptan experienced by clinicians. We should address the mechanisms to explain the discrepancy between the EVEREST trial and a favorable clinical outcome experienced in Japan.

The SMILE study, a post-marketing surveillance of tolvaptan, demonstrated from data of consecutive patients who had received tolvaptan between 2011 and 2015, that 43.6% of patients continued tolvaptan therapy for over two weeks in real-world clinical practice [3]. Also, 48.6% were aged over 80 years. Their clinical signs in lower limb edema, pulmonary congestion, dyspnea, third sound, and rales improved statistically significantly after two weeks, but the number of improvements were clinically subtle, which may indicate that a considerable number of "non-responders" might be included.

Considering these observations, elder population, responses to tolvaptan, and renal function may be keys to successful long-term tolvaptan therapy.

Elderly populations

Almost half of the patients receiving tolvaptan therapy are aged over 80 years old [3] and we should understand the efficacy and safety of tolvaptan therapy in this population. The subanalysis of SMILE study demonstrated that the effectiveness of tolvaptan therapy in patients aged over 80 years old was similar to that in younger patients [21]. Similar favorable results were also reported in other studies. Kinoshita and colleagues demonstrated that tolvaptan therapy in patients aged over 80 years old with repeated HF hospitalizations resulted in immediate decongestion and reduced hospitalization period with a lower incidence of worsening renal function [22]. In another study, patients aged over 85 years old had similar rate of worsening renal function and length of hospitalization stay compared with those aged under 85 years old during tolvaptan therapy [23].

Nevertheless, special attention should be paid to the patient's symptoms to avoid hypernatremia, because the incidence rate of thirst was lower in the aged patients in the sub-analysis of SMILE study [21]. We recently proposed a scoring system to predict the occurrence of hypernatremic events, and age is a strong risk factor for hypernatremia, particularly when tolvaptan was administered at a high dose (i.e. 15 mg/day) [24]. A low starting dose (i.e. 3.75 mg/day) with careful monitoring of symptoms and surveillance of serum sodium level, particularly during the first week, would be recommended for elder populations.

Responder

We sometimes experience non-responders to tolvaptan therapy, whose urine volume remains unchanged and their clinical courses do not improve [25,26]. We previously proposed urine osmolality and urine aquaporin-2 level as a predictor of response to tolvaptan [27]. In a fasting condition before taking any diuretics, the secretion of vasopressin is stimulated and the urine osmolality is in general increased due to reabsorption of pure water via activated aquaporin-2, which is located at the principal cells in the kidney (Fig. 1) [28]. After the administration of tolvaptan, which antagonizes vasopressin type-2 receptor, activity of aquaporin-2 is inhibited and aquauresis is enhanced. As a result, urine osmolality and urine aquaporin-2 level at baseline are high in the healthy populations, i.e. responders, and decrease significantly following tolvaptan administration (Fig. 2). In non-responders, urine osmolality and urine aquaporin-2 excretion remain lower irrespective of administration of tolvaptan, because of deterioration in collecting duct function (Fig. 2).

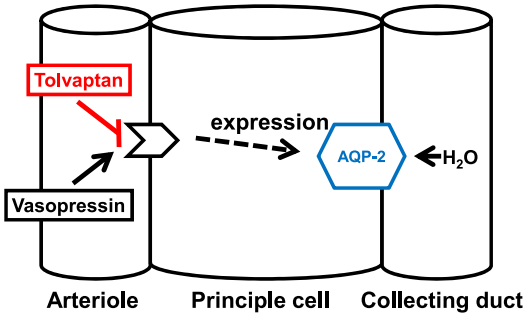

Fig. 1. Mechanism of free water reabsorption and its blockage by tolvaptan in the kidney. Excreted vasopressin binds receptors located on the surface of principal cell, and stimulates the expression and activation of aquaporin-2, which facilitates the reabsorption of free water from the collecting duct and increases urine osmolality. When tolvaptan is administered, it inhibits the signal cascade of water reabsorption by antagonizing vasopressin receptor. Then, the excretion of aquaporin-2 in urine and urine osmolality decrease. *Abbreviations*: AQP-2, aquaporin-2; H_2O, water.

Our team previously demonstrated that the urine aquaporin-2-defined responders had higher freedom from HF readmissions when administered tolvaptan for 2 years, whereas the tolvaptan therapy did not improve outcomes in the non-responders (Fig. 3) [27]. As a result, tolvaptan therapy reduced the total medical expense in the responders but not in the non-responders [29]. A prospective study of long-term tolvaptan therapy in predicted responders is ongoing [30].

Renal function

Many patients receiving tolvaptan therapy had renal dysfunction [3], which is associated with worse prognosis. Preservation of

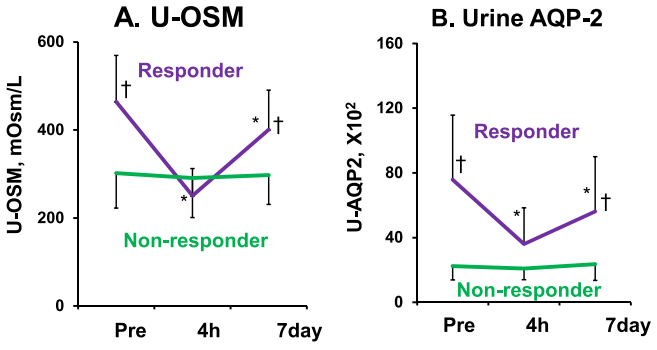

Fig. 2. Changes in urine osmolality (A) and urine aquaporin-2 level (B) between responders and non-responders before and after tolvaptan administration [25,37]. *Abbreviations*: U-OSM, urine osmolality; AQP-2, aquaporin-2; Pre, just before tolvaptan initiation; 4 h, 4 hours after tolvaptan initiation; 7 days, 7 days following the initiation of tolvaptan therapy. $^{*}p < 0.05$ compared with baseline (Pre) by Tukey's test and repeated analyses of variance. $^{\dagger}p < 0.05$ by unpaired *t*-test compared with non-responders.

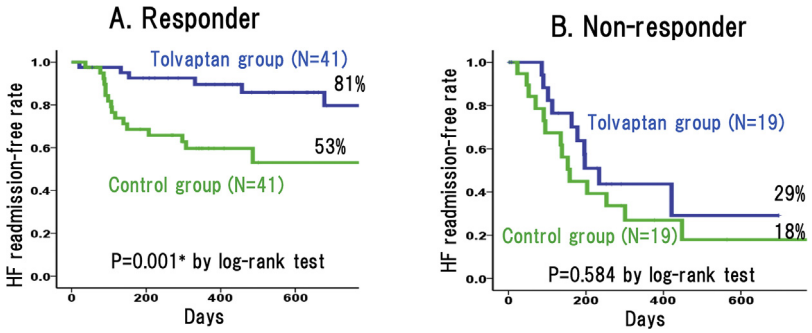

Fig. 3. Heart failure (HF) readmission-free rate between tolvaptan group and control group in the responder (A) and non-responder (B) [27]. *$p < 0.05$ by log-rank test. Response to tolvaptan is defined by urine aquaporin-2 level.

renal function is a key to better prognosis in HF patients. Table 2 summarizes the results of six long-term tolvaptan therapy studies, including four Japanese ones [27,31–34]. Tolvaptan dose ranges were 4.9–9.8 mg/day in four Japanese studies, whereas two studies in other countries were performed at 30 mg/day [20,35]. Furosemide was administered approximately at 30–60 mg/day with tolvaptan in four Japanese studies, but was administered at 52.1 mg/day or 73.0 mg/day with tolvaptan in two studies in other countries.

Fig. 4A summarizes the relationship between the dose of furosemide concomitantly administered with tolvaptan at discharge and the relative risk reduction in six enrolled studies. A lower dose of furosemide at discharge was strongly correlated with higher risk reduction ($r^2 = 0.7472$).

Table 3 summarizes the change in serum creatinine concentration at the late phase (Δcreatinine) in five studies (one study lacked follow-up data on renal function) [20,27,31,32,34,35]. Increase in Δcreatinine was lower in the tolvaptan group than the control group among all three Japanese studies; whereas Δcreatinine was similar between groups in another study and was rather higher in the tolvaptan group in a further study. In summary, lower furosemide dose at discharge was associated with less increase in serum creatinine level ($r^2 = 0.6158$, Fig. 4B).

In summary of this meta-analysis, lower furosemide dose and increased preservation of renal function may be keys to better clinical outcome during tolvaptan therapy. These results may also explain the discrepancy between the unfavorable results in the EVEREST study and the favorable results in Japanese studies.

Current recommendation for therapeutic strategy for long-term tolvaptan administration

Patients with congestive HF who are admitted due to worsening of congestion refractory to over 40 mg/day of furosemide may receive tolvaptan at an initial dose of 3.75–7.5 mg/day within several days. The measurement of biomarkers including urine osmolality is highly recommended to predict response to tolvaptan prior to the initiation of tolvaptan [25]. Patients with renal dysfunction or hyponatremia, or those with a history of repeated hospitalizations due to worsening HF are good candidates for tolvaptan therapy [30].

Table 2
Summary of six studies assessing the implication of long-term tolvaptan therapy.

	TLV dose (mg/day)	Furosemide dose (mg/day)*		LVEF	Incidence rate (follow-up duration)		Relative risk reduction	*p*-Value
		TLV	Control		TLV	Control		
Imamura (2014, 2015) [27,31]	4.9	54.2 → 43.3 at 1 Mo	46.2 → 45.8 at 1 Mo	32.6%	Death or HF admit (2 yr)		37.5%	0.009
					45%	72%		
Uemura (2017) [34]	7.2	64.6 → 63.9	63.2 → 92.5	46.5%	Cardiac death or HF admit (12 Mo)		31.4%	0.035
					42.9%	62.5%		
Nakano (2018) [32]	9.8	40.6 → 36.5	41.5 → 47.6	49.5%	Death or HF admit (18 Mo)		39.3%	0.034
					44.1%	72.7%		
Nakamura (2018) [33]	8.1	68.8 → 30.4	31.6 → 28.4	43.0%	Death or HF admit (20 Mo)		58.5%	0.234
					14.8%	35.7%		
Udelson (2007) [35]	30	52.2 → 52.1 at 1 wk	62.5 → 64.1 at 1 wk	23.3%	Death or HF admit (1 yr)		41.5%	0.0272
					20.0%	34.2%		
Konstam (2007) [20]	30	114.9 → 73.0	109.8 → 75.7	27.5%	Cardiac death or admit (9.9 Mo)		−4.5%	0.55
					42.0%	40.2%		

* Dose at baseline and discharge.
TLV, tolvaptan; LVEF, left ventricular ejection fraction; HF, heart failure.

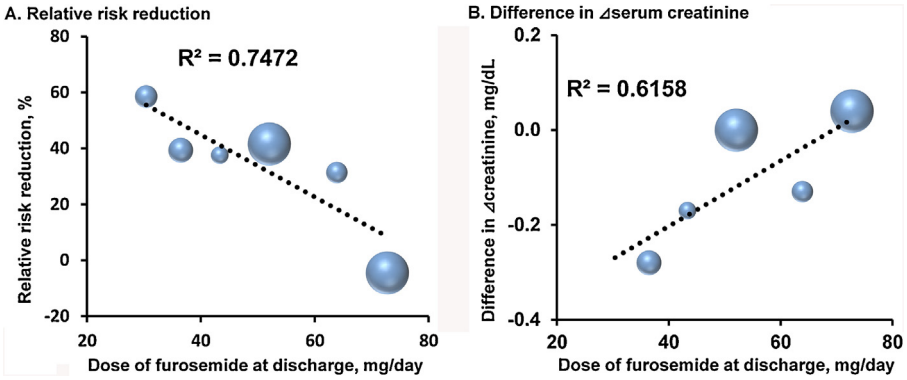

Fig. 4. The effects of furosemide dose at discharge on relative risk reduction (A) and change in serum creatinine concentration (B) during long-term tolvaptan therapy. Δ creatinine, change in serum creatinine concentration during the observational period.

Table 3
Changes in serum creatinine concentration at late phase in long-term tolvaptan studies.

	Tolvaptan dose (mg/day)	Change in serum creatinine concentration (mg/dL)	
		Tolvaptan group	Control group
Imamura (2014, 2015) [27,31]	4.9	+0.03 (1M)	+0.2 (1M)
Uemura (2017) [34]	7.2	−0.06 (6M)	+0.07 (6M)
Nakano (2018) [32]	9.8	−0.01 (6M)	+0.27 (6M)
Udelson (2007) [35]	30	0 ± 0.2 (28W)	0 ± 0.4 (28W)
		0 ± 0.3 (54W)	0 ± 0.3 (54W)
Konstam (2007) [20]	30	+0.02 (4W)	0.0 (4W)
		+0.07 (24W)	+0.03 (24W)
		+0.10 (48W)	+0.05 (48W)

At discharge, we should attempt to reduce the dose of furosemide down to 40 mg/day, considering long-term prognosis [36]. Patients satisfying above conditions may continue tolvaptan therapy in the ambulatory situation to prevent worsening of renal function and HF readmissions.

Conclusion

Tolvaptan is a strong tool for the treatment of acute HF when used appropriately. A prospective randomized controlled study to administer tolvaptan in responders with an appropriate reduction in the dose of concomitant diuretics may demonstrate the long-term efficacy of tolvaptan therapy.

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