

# An overview of satavaptan: a selective V2 receptor antagonist

Satavaptan is a new selective V2 receptor antagonist that shares the aquaretic effect of the other arginine vasopressin antagonists. Its usefulness has been demonstrated in the correction of hyponatremia as well as in fluid removal in patients with cirrhosis. In addition, animal studies have suggested promising effects in the treatment of several other conditions, such as polycystic kidney disease, renal cell carcinoma, glaucoma, diabetic nephropathy and urinary tract infections. This article reviews the various animal and human studies that have outlined its potential clinical role and provided direction for further research with this drug.

**KEYWORDS:** arginine vasopressin antagonist ■ cirrhosis ■ hyponatremia ■ satavaptan

The increasing recognition of the risk of hyponatremia and its public health impact [1–4] has been matched by increasing interest in the new class of drugs, proven to correct hyponatremia, the arginine vasopressin (AVP) V2 receptor antagonists (so-called vaptans).

Two vaptans have already been approved for the management of hyponatremia in the USA, and considerable research efforts have been devoted to develop other vaptans.

This article details the basic, animal and human studies of the AVP antagonist satavaptan.

## Arginine vasopressin

Arginine vasopressin plays a major role in plasma Na<sup>+</sup> regulation [5]. It is a hormone that is mainly synthesized in the hypothalamic paraventricular and supraoptic nuclei and stored in the posterior pituitary gland [2]. AVP release is normally controlled by serum osmolality. Changes in serum osmolality are sensed by special osmoreceptors [6] and an increase in serum osmolality by as little as 1% triggers the release of AVP [7]. In addition, a drop in blood volume is sensed by baroreceptors, resulting in stimulation of AVP secretion through a cascade of mechanisms [8]. Moreover, angiotensin II that is synthesized through the rennin–angiotensin–aldosterone system directly stimulates the release of AVP [9,10].

## AVP receptors

The actions of AVP are mediated by binding to a group of different receptor isoforms. These receptors are classified into three different subtypes. V1A receptors are found mainly on the vascular smooth muscle cells, where

AVP stimulation results in vasoconstriction [11,12]. V1B receptors are expressed on the cells of the anterior pituitary gland and throughout the brain [13] and, when stimulated, they mediate acetylcholine (ACTH) release [14,15]. V2 receptors are located mainly on the principal cells of the collecting ducts of the kidneys and, by binding to it, AVP allows water reabsorption [11,16]. AVP stimulation of V2 receptors that are located in the basolateral membrane of the renal tubular cells activates adenylate cyclase, leading to increased concentration of cyclic-3'-5'-adenosine monophosphate (cAMP), as well as activation of protein kinase A (PKA). PKA triggers the water channel aquaporin 2 (AQP2)-containing vesicles to fuse with the luminal plasma membrane of the collecting duct, thereby allowing water to enter the cell [17]. Passive resorption of water through the basolateral membrane (AQP3 and AQP4) along osmotic gradients by way of other water channels into the vasa recta completes the process of reabsorption [17].

## Pharmacology of satavaptan

The chemical structure of satavaptan (SR121463) is 1-[4-(*N*-tert-butylcarbamoyl)-2-methoxybenzene sulfonyl]-5-ethoxy-3-spiro[4-(2-morpholinoethoxy)cyclohexane]indol-2-one. It was synthesized in Sanofi Recherche, Toulouse, France [18].

SR121463 is an orally active, nonpeptide antagonist of AVP V2 receptors. It has been studied in different animal species (mice, rats, dogs, rabbits, bovines, monkeys and pigs) and humans. SR121463 displayed a high competitive affinity for AVP V2 receptors

Jareer Farah<sup>1</sup>,  
Suleiman Daifallah<sup>2</sup>,  
Hammam Zmily<sup>1</sup>  
& Jalal K Ghali<sup>1\*</sup>

<sup>1</sup>Detroit Medical Center,  
Wayne State University, Detroit,  
MI, USA

<sup>2</sup>Wayne State University/John D Dingell  
VA Medical Center, Detroit, MI, USA

\*Author for correspondence:

Tel.: +1 313 745 7061

Fax: +1 313 745 9021

jghali@dmc.org

future  
medicine part of fsg

( $0.6 \leq K_i \leq 4.1$  nM); it inhibits, in a dose-dependent manner, the AVP-specific binding to kidney medullo-papillary membranes of rat, bovine and human origin with nanomolar and even subnanomolar potency ( $K_i$  values of 1.42, 0.64 and 4.1 nM, respectively). SR121463 exhibits only weak affinities for other AVP and oxytocin (OT) receptors; it interacts with at least a 100-fold lower potency with V1A, V1B and OT receptors than with V2 receptors, explaining its highly specific and selective V2 receptor antagonist activity [18–21].

The aquaretic effect of satavaptan was noted in multiple animal and human studies following oral and intravenous administration. It induces a dose-dependent increase in the urine flow rate (water clearance) and a decrease in urine osmolality (Uosm) without major changes in urinary  $\text{Na}^+$  and  $\text{K}^+$  excretion over a 24-h period following the drug administration.

In an experiment in normally hydrated conscious rats by Serradeil Le Gal, SR121463 was administered intravenously at doses ranging from 0.003 to 0.3 mg/kg, and orally at doses ranging from 0.03 to 10 mg/kg. Both routes of administration induced a dose-dependent increase in the urine flow rate and decrease in Uosm. The intravenous dose was five-times more potent than the oral dose, an effect consistent with good bioavailability for SR121463 [18].

The maximum effect was reached in a 2-h period after oral administration of different doses of SR121463. The higher doses (3–10 mg/kg) had an effect lasting 6–24 h after administration in normally hydrated conscious rats [18].

In a clinical trial in humans, satavaptan was reported to have a long half-life of 14–17 h, with maximum plasma concentrations 3 h after dosing. The mean plasma concentration increased with dosage and duration of drug administration and stabilized on day 5 [22]. SR121463 was 94.5–96% bound to plasma proteins and its major route of excretion in animals was via feces.

### Safety of satavaptan

Safety pharmacology studies demonstrated that SR121463 was well tolerated in mice, rats and dogs with no major effects on cardiovascular and respiratory function, central and autonomic nervous systems, hydro-electrolytic balance and gastrointestinal function. SR121463 was evaluated for general toxicity in single and repeated administration studies in rodents and nonrodent

species. Effects attributable to the pharmacological V2R action of SR121463 (i.e., dehydration due to exaggerated pharmacological activity at AVP V2 receptors) were reported. Intravenous and oral safety margins, based on pharmacologically active dosages and no observed effect dosages for target organ toxicity, are over 100-fold for rats.

No genotoxicity or mutagenicity was observed in the Ames and DNA repair tests *in vitro* [20].

### Effects of satavaptan in hyponatremia

Antagonism of the V2 receptor increases free water excretion causing hypoosmolar urine, enhanced diuresis and increased serum  $\text{Na}^+$  levels.

#### ■ Animal studies

Several animal studies on satavaptan were consistent with the aforementioned effects and have demonstrated the aquaretic effect of satavaptan (TABLE 1) [23–28]. In an experiment by Lacour *et al.* [26], acute oral administration of SR121463 to rats induced a dose-dependent aquaresis accompanied by an increase in AVP and aldosterone excretion. This early hormonal increase was a compensatory mechanism for the increase in plasma osmolality. This is consistent with the earlier observation: a 1% change in plasma osmolality could change plasma AVP concentration by 1 pg/ml in healthy subjects [29]. However, with chronic treatment, urine volume and aldosterone excretion fell by 40% while urine AVP remained constant. In another experiment by Perucca *et al.* [30], intraperitoneal injection of satavaptan in rats induced natriuretic effect within the first 4–6 h of treatment. This natriuretic effect remained far smaller than its diuretic effect and sevenfold less than that induced by furosemide. Moreover, the natriuretic effect was not apparent in the 24-h urine sample as compensatory  $\text{Na}^+$  retention occurred after initial  $\text{Na}^+$  loss. This small natriuretic effect of V2 receptor antagonists during the first 4–6 h was also observed in other studies [26,31].

#### ■ Human studies

In a multicenter, randomized, double-blind, placebo-controlled study, Soupart *et al.* studied the effect of satavaptan in patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [22]. This study had a short- and long-term part; the short-term had two phases. In the 5-day double-blind phase, nine

Table 1. Animal studies showing the aquaretic effect of satavaptan.

Study	Species	Condition of species	Intervention	Results	Ref.
Serradell-Le Gal <i>et al.</i>	Rats (male Sprague-Dawley)	Normal, conscious	<ul style="list-style-type: none"> <li>0.003–0.3 mg/kg iv. (n = 6)</li> <li>0.03–10 mg/kg oral SR121463A (n = 7) or 10 mg/kg OPC-31260 (n = 8) or 30 mg/kg furosemide (n = 8) or 30 mg/kg hydrochlorothiazide (n = 8) or vehicle (n = 20)</li> </ul>	<ul style="list-style-type: none"> <li>Oral SR121463A and OPC-31260 caused a dose-dependent increase in Uv and reduction in Uosm</li> <li>iv. SR121463A increased Uv</li> <li>Both hydrochlorothiazide and furosemide increased Uv, but also increased urine Na<sup>+</sup> and K<sup>+</sup> excretion</li> <li>SR121463A increased Uv and decreased Uosm</li> <li>SR121463A is a V2 antagonist without intrinsic agonistic activity</li> </ul>	[19]
Serradell-Le Gal <i>et al.</i>	Rats (male BB)	Central hereditary DI	<ul style="list-style-type: none"> <li>10 mg/kg ip.</li> </ul>	<ul style="list-style-type: none"> <li>SR121463A increased Uv and decreased Uosm</li> <li>SR121463A is a V2 antagonist without intrinsic agonistic activity</li> </ul>	[19]
Shen <i>et al.</i>	Rats (Sprague-Dawley)	16 normal rats divided equally between treatment and control groups	<ul style="list-style-type: none"> <li>Twice-daily dose of 0.3 mg/kg ip. SR121463A or vehicle</li> </ul>	<ul style="list-style-type: none"> <li>SR121463A decreased urinary concentrating ability</li> <li>No significant change in mRNA of V2 receptor or AC in SR121463A and control groups</li> </ul>	[23]
Huang <i>et al.</i>	Rats (adult male Munich-Wistar-Frömter)	Anesthetized	<ul style="list-style-type: none"> <li>0.3 mg/kg iv. SR121463B or vehicle</li> </ul>	<ul style="list-style-type: none"> <li>Decrease in the whole kidney fractional reabsorption of fluid</li> <li>A greater than tenfold higher urinary flow rate and increase in electrolyte-free-water clearance</li> <li>Significant fall in Uosm</li> <li>Minor decreases in kidney fractional reabsorption of Na<sup>+</sup> and Cl<sup>-</sup></li> <li>No effect on HR and MAP</li> <li>Acute retrieval of AQP2 water channel protein from the apical plasma membrane to vesicle-like structures in the cytoplasm</li> <li>No effect on the thick ascending loop of Henle. It starts its effect in the early distal tubule</li> </ul>	[24]
Promeneur <i>et al.</i>	Rats (adult female BB); rats (Wistar)	BB rats with central DI; normal Wistar rats	<ul style="list-style-type: none"> <li>0.4 mg/rat SR121463A was subcutaneously injected into BB rats q12 h for 24 or 48 h. Control BB rats had saline injections</li> <li>Subsequently, the total kidney AQP2 protein levels and kidney inner medullary AQP2 mRNA levels were determined from five experimental and five control rats. From another seven experimental rats and seven control rats, kidney inner medullary AQP2 and phosphorylated AQP2 protein levels were determined</li> </ul>	<ul style="list-style-type: none"> <li>BB rats had higher urine output in response to 24-h treatment with SR121463A. After 48 h of treatment, urine output remained markedly elevated</li> <li>There was a marked decrease in AQP2 protein levels in kidney inner medulla, total kidney AQP2 protein levels and AQP2 mRNA from BB rats treated with SR121463A compared with control rats. Thus, AQP2 expression is dependent on AVP-V2 receptor activation</li> </ul>	[25]

AC: Adenylyl cyclase; AVP: Arginine vasopressin; BB: Brattleboro; DI: Diabetes insipidus; HR: Heart rate; ip.: Intraperitoneal; iv.: Intravenous; MAP: Mean arterial pressure; OT: Oxytocin; PKC: Protein kinase C; Uosm: Urine osmolality; Uv: Urine volume.

Table 1. Animal studies showing the aquaretic effect of satavaptan (cont.).

Study	Species	Condition of species	Intervention	Results	Ref.
Lacour <i>et al.</i>	Rats (male Sprague-Dawley)	Normal	<p>Experiment I:</p> <ul style="list-style-type: none"> <li>Effect of SR121463 after acute oral treatment:                             <ul style="list-style-type: none"> <li>Rats given SR121463 0.3–3 mg/kg or vehicle.</li> <li>Water intake from 0 to 6 h and from 6 to 24 h measured along with Uosm, urine Na<sup>+</sup>, K<sup>+</sup>, AVP and aldosterone excretion</li> </ul> </li> </ul> <p>Experiment II:</p> <ul style="list-style-type: none"> <li>Aquaretic and hormonal effects of SR121463 during chronic oral treatment (28 days): 11 rats got once-daily SR121463 3 mg/kg/day for 28 days and 11 rats had vehicle</li> </ul>	<p>Experiment I:</p> <ul style="list-style-type: none"> <li>Dose-dependent aquaresis that was accompanied by Na<sup>+</sup>, K<sup>+</sup>, aldosterone and AVP excretion over 6 h after dosing</li> <li>Solute excretion decreased from 6 to 24 h. Over 24 h, net solute excretion was similar to the control group</li> <li>hemocentration and increases in plasma angiotensin II and adrenocorticotrophin hormone at 2 h after dosing</li> </ul> <p>Experiment II:</p> <ul style="list-style-type: none"> <li>Chronic treatment with SR121463 induced a marked aquaresis associated with aldosterone and vasopressin excretion</li> <li>After a week of treatment, urine volume and aldosterone excretion were reduced by 40% and then stabilized. Urine vasopressin excretion and Uosm remained constant throughout the study:                             <ul style="list-style-type: none"> <li>One day after the 28th administration of SR121463, plasma osmolality and plasma Na<sup>+</sup> returned to their control levels</li> <li>No significant changes in binding parameters with chronic treatment</li> <li>Number and dissociation constant for V2 receptors in rat kidneys remained unchanged with chronic treatment with SR121463</li> </ul> </li> </ul>	[26]

AC: Adenylyl cyclase; AVP: Arginine vasopressin; BB: Brattleboro; DI: Diabetes insipidus; HR: Heart rate; ip.: Intraperitoneal; iv.: Intravenous; MAP: Mean arterial pressure; OT: Oxytocin; PKC: Protein kinase C; Uosm: Urine osmolality; Uv: Urine volume.

Table 1. Animal studies showing the aquaretic effect of satavaptan (cont.).

Study	Species	Condition of species	Intervention	Results	Ref.
Pouzet <i>et al.</i>	Rats (BB for experiment A, B and D); rats (male Sprague-Dawley for experiment C)	With Di; normal	<p>Experiment A1:</p> <ul style="list-style-type: none"> <li>Five rats received SR121463A 10 mg/kg ip., four rats had vehicle</li> </ul> <p>Experiment A2:</p> <ul style="list-style-type: none"> <li>24 rats divided into four equivalent groups received SR121463A ip. injections of 0.001–10 mg/kg or vehicle in random fashion. The same rats received different doses of drug or vehicle on different days. Five rats also received one dose of OPC31260 10 mg/kg</li> </ul> <p>Experiment B:</p> <ul style="list-style-type: none"> <li>Nine rats received SR121463A and nine rats 0.6% methylcellulose daily in gastric lavage for 8 days</li> </ul> <p>Experiment C:</p> <ul style="list-style-type: none"> <li>Six rats were gavaged daily for 7 days with SR121463A 3 mg/kg in 0.6% methylcellulose, six rats gavaged with 0.6% methylcellulose daily for 7 days plus SR121463A 3 mg/kg that was added to food, or six rats gavaged daily for 7 days with 0.6% methylcellulose alone</li> </ul> <p>Experiment D:</p> <ul style="list-style-type: none"> <li>A total of 19 rats divided into three equivalent groups of six or seven rats. Two groups had a pump inserted in the peritoneal cavity that delivered OT at a rate of 3 µg/kg/h. The third group was sham-operated. On the fourth day of OT treatment, one of the two groups received an ip. injection of SR121463A 1 mg/kg and the other two groups received saline injection</li> </ul>	<p>Experiment A1:</p> <ul style="list-style-type: none"> <li>Decline in Uosm</li> <li>Doubling of urine flow rate</li> <li>Increase in solute free water excretion</li> <li>No change in total solute excretion</li> </ul> <p>Experiment A2:</p> <ul style="list-style-type: none"> <li>Significant effect on Uosm and solute-free water clearance was detected as low as SR121463A 0.01 mg/kg</li> <li>Urine flow rate was statistically significant at dose of SR121463A 0.1 mg/kg</li> <li>Uosm is more sensitive than urine flow rate</li> <li>OPC31260 was much less potent than SR121463A</li> </ul> <p>Experiment B:</p> <ul style="list-style-type: none"> <li>Oral SR121463A caused increase in urine flow rate, decrease in Uosm and increased free water excretion</li> </ul> <p>Experiment C:</p> <ul style="list-style-type: none"> <li>Intermediate dose of SR121463A at 3 mg/kg caused iso-osmolar urine and increased urine flow rate</li> <li>The aquaretic effect of SR121463A with gavage or with food was the same</li> <li>Extrarenal water losses were doubled suggesting that V2 receptor blockade affects water turnover in organs other than the kidney</li> </ul> <p>Experiment D:</p> <ul style="list-style-type: none"> <li>SR121463A abolished that antidiuretic effect of OT</li> <li>OT exerts its effect by binding to V2 receptors</li> </ul>	[27]
Yao <i>et al.</i>	Rats (male)	PKC- $\alpha$ -deficient (-/-), PKC- $\alpha$ control rats	<ul style="list-style-type: none"> <li>SR121463</li> </ul>	<ul style="list-style-type: none"> <li>SR121463 lowers Uosm to comparable hypotonic levels in PKC-<math>\alpha^{-/-}</math> and PKC-<math>\alpha^{+/+}</math> mice.</li> </ul>	[28]
Perucca <i>et al.</i>	Rats (Wistar)	Normal conscious	<ul style="list-style-type: none"> <li>ip. injection of various concentrations of SR121463A in six rat groups. Urine collection for 6 h and then for 18 h</li> <li>Comparison of various doses of SR121463A and furosemide</li> </ul>	<ul style="list-style-type: none"> <li>Dose-dependent increase in urine Na<sup>+</sup> and much more diuresis. Increase in K<sup>+</sup> excretion was not statistically significant</li> <li>The aquaretic but not the natriuretic effect remained detectable over 24 h. Thirst and thus fluid intake increased during the whole duration of the V2 receptor blockade</li> <li>Induced a natriuresis sevenfold smaller than did furosemide</li> </ul>	[30]

AC: Adenylyl cyclase; AVP: Arginine vasopressin; BB: Brattleboro; Di: Diabetes insipidus; HR: Heart rate; ip.: Intraperitoneal; iv.: Intravenous; MAP: Mean arterial pressure; OT: Oxytocin; PKC: Protein kinase C; Uosm: Urine osmolality; Ur: Urine volume.



Table 1. Animal studies showing the aquaretic effect of satavaptan (cont.).

Study	Species	Condition of species	Intervention	Results	Ref.
Jimenez et al.	Rats (adult male Wistar)	20 with cirrhosis and ascites; 23 normal in control group	Group 1: • Intragastric SR121463 0.5 mg/kg in 0.6% methylcellulose and water daily for 10 days (ten cirrhotic and 11 control rats) Group 2: • Intragastric 0.6% methylcellulose in water at 4.2 ml/kg (ten cirrhotic and 11 control rats)	<ul style="list-style-type: none"> <li>• No change in urinary flow after receiving SR121463 in the control group. However, these animals had a significant decrease in Uosm in the first day of treatment</li> <li>• SR121463 increased urine flow rate and decreased Uosm in cirrhotic rats throughout the 10-day study. In addition, a natriuretic effect was produced that disappeared after the first day of treatment</li> <li>• Cirrhotic rats with ascites receiving the aquaretic agent showed a significantly higher percentage of water load excreted and lower Uosm than cirrhotic animals receiving the vehicle and normalization in serum Na<sup>+</sup> concentration and osmolality</li> </ul>	[32]

AC: Adenylyl cyclase; AVP: Arginine vasopressin; BB: Brattleboro; DI: Diabetes insipidus; HR: Heart rate; ip.: Intraperitoneal; iv.: Intravenous; MAP: Mean arterial pressure; OT: Oxytocin; PKC: Protein kinase C; Uosm: Urine osmolality; Uv: Urine volume.

patients received placebo, 14 patients received satavaptan 25 mg/day and 12 patients received satavaptan 50 mg/day. A total of 34 patients with serum Na<sup>+</sup> concentration between 115 and 132 mmol/l completed the double-blind phase. Responders to this treatment were defined as patients who achieved normalization of serum Na<sup>+</sup> concentration within a range of 135–145 mmol/l, or an increase in serum Na<sup>+</sup> concentration by at least 5 mmol/l from baseline over at least 24 h during the double-blind period. Both satavaptan groups achieved dose-related higher serum Na<sup>+</sup> concentration compared with placebo (136 ± 3 mmol/l in the 25-mg group [p = 0.011] and 140 ± 6 mmol/l in the 50-mg group [p < 0.0001], compared with 130 ± 5 mmol/l in the placebo group). Responders were 79% (11 out of 14 patients) in the 25-mg group, 83% (ten out of 12 patients) in the 50-mg group and 13% (one out of eight patients) in the placebo group. Median times to reach response in serum Na<sup>+</sup> concentration were 63 h (p = 0.010) and 30 h (p = 0.002) for satavaptan 25 and 50 mg/day, respectively. The median time was over 120 h for the placebo group.

Both satavaptan groups achieved significantly more diuresis than placebo at the end of the double-blind period, as measured by the 6-h postdose diuresis: 573 ± 423 ml in the 25-mg group and 488 ± 392 ml in the 50-mg group, compared with 10 ± 179 ml in the placebo group. The drop in Uosm at the end of the double-blind phase, as measured by the 6-h postdose Uosm, was only statistically significant in the satavaptan 50 mg/day group (p = 0.044 vs placebo). At the end of the double-blind period, there was no significant change from baseline in body-weight, thirst index, fluid intake, plasma AVP and plasma renin in both satavaptan-treated groups compared with placebo.

A total of 34 patients entered a 23-day open-label phase. During the open-label adjustment period, mean serum Na<sup>+</sup> concentration remained in the normal range (137 ± 4 mmol/l). There were 79% of patients that received 25 mg/day of the compound.

Out of the 34 patients who entered the short-term study, 18 patients were included in the long-term study (at least 12 months). The patients received satavaptan 12.5, 25 or 50 mg/day based on serum Na<sup>+</sup> concentration. The mean serum Na<sup>+</sup> concentrations were 138 ± 3, 138 ± 5 and 140 ± 3 mmol/l at 6, 8 and 12 months, respectively. No adverse events related to satavaptan were noted during this period.

The safety of satavaptan was assessed during the double-blind phase of the study. Five patients in the 25-mg and four in the 50-mg group had over 8 mmol/l increase in serum Na<sup>+</sup> concentration within 24 h after the first dose. One patient in the 50-mg group had an increase of over 18 mmol/l in 48 h. One patient in the 25-mg group experienced mild intensity vomiting.

During the double-blind period, two patients (one in the 25-mg and one in the 50-mg group) developed hypernatremia with serum Na<sup>+</sup> concentrations of 146 and 156 mmol/l, respectively. The satavaptan 25-mg patient had mild intensity vomiting that resolved spontaneously while the other patient was asymptomatic. During the open-label period, five patients (four in the 25-mg and one in the 50-mg group) developed hypernatremia (Na<sup>+</sup> concentration between 146 and 161 mmol/l). One patient on satavaptan 25 mg had nausea, rigors and confusion, and the other four were asymptomatic.

During the overall exposure to satavaptan (double-blind and open-label periods), 18 (51%) patients experienced at least one adverse event. In one patient only, the investigator considered the adverse events (polyuria, nausea, moderate rigors and confusion) related to the study treatment. Seven (20%) patients had serious adverse events including sepsis (leading to death), respiratory failure (with recovery), bronchitis (with recovery), gastrointestinal hemorrhage (leading to death), vasculitis (leading to death), pneumonia (leading to death) and malignant brain neoplasm (leading to death).

None of the serious adverse events were considered by the investigators to be related to the study treatment. Other adverse events not related to satavaptan treatment were urinary tract infection (one patient in each of the 25- and 50-mg groups), vomiting (one patient in

the 25-mg group), pruritus (one patient in the 25-mg group), and one patient had stomatitis and one had cryoglobulinemia in the placebo group. Overall, three (9%) patients withdrew from the study treatment as a result of serious adverse events (see TABLE 2 for other side effects).

### Role of satavaptan in cirrhosis

#### ■ Animal studies

The use of satavaptan in cirrhosis was tested in one animal model. Jimenez *et al.* showed that cirrhotic rats receiving satavaptan had a higher urine flow rate and lower U<sub>osm</sub> with normalization in serum Na<sup>+</sup> concentration and serum osmolality [32].

#### ■ Human studies

Previous studies have shown that V2 receptor antagonists are effective in improving serum Na<sup>+</sup> concentration in patients with cirrhosis, ascites and dilutional hyponatremia [33–35].

The use of satavaptan in cirrhosis has been tested in two prospective, multicenter, randomized, double-blind, placebo-controlled studies by Gines *et al.*, one study in hyponatremic patients [36] and one study in patients without significant hyponatremia [37].

In the first study, 145 patients with evidence of cirrhosis by biopsy or combination of clinical, biochemical, ultrasonographic and endoscopic findings were screened. All had moderate or tense ascites and a serum Na<sup>+</sup> concentration of 130 mmol/l or lower.

Patients entered a 5–7-day screening period during which they received spironolactone at 100 mg/day. After screening, 35 patients were excluded for different reasons. The remaining 110 patients were randomized to a 14-day treatment of single daily dose placebo (28 patients), satavaptan 5 mg/day (28 patients), 12.5 mg/day (26 patients) and 25 mg/day (28 patients). Out of 110 patients, 99 completed the study.

**Table 2. Changes in blood pressure, heart rate and sodium levels in hyponatremic patients treated with satavaptan versus placebo.**

Changes	Double-blind period		
	Placebo (n = 9)	25 mg (n = 14)	50 mg (n = 12)
Mean decrease in standing systolic blood pressure (mmHg)			6 ± 23
Mean decrease in standing diastolic blood pressure (mmHg)			8 ± 14
Patients with orthostatic hypotension (%)	4 (44%)	8 (67%)	5 (50%)
Mean change in heart rate (beats per min)	6 ± 23	6 ± 14	2 ± 10
Patients with increase in serum sodium >8 mmol/l within 24 h		5	4
Patients with increase in serum sodium >18 mmol/l within 48 h			1
Patients developed hypernatremia (serum Na <sup>+</sup> concentration ≥145 mmol/l)		1	1

Data taken from [23].

The first primary efficacy end point was the change in bodyweight from baseline (day 1) to the end of the study treatment period (day 14). There was less weight gain with the satavaptan 5-mg group ( $0.15 \pm 4.23$  kg) compared with placebo ( $0.49 \pm 4.99$  kg), and even weight loss with 12.5 and 25 mg/day ( $-1.59 \pm 4.6$  and  $-1.68 \pm 4.98$  kg, respectively;  $p = 0.05$ ). There were no significant differences between the three groups of patients treated with satavaptan and the group of patients treated with placebo.

The other primary efficacy end point was the change in serum  $\text{Na}^+$  concentration from baseline (day 1) to day 5;  $1.3 \pm 4.2$ ,  $4.5 \pm 3.5$ ,  $4.5 \pm 4.8$  and  $6.6 \pm 4.3$  mmol/l for the placebo, satavaptan 5, 12.5 and 25 mg/day groups, respectively ( $p < 0.01$ ).

The effects on secondary efficacy end points were consistent. Satavaptan 5, 12.5 and 25 mg/day had greater reduction in abdominal girth from baseline to the end of the study treatment compared with placebo ( $0.0 \pm 6.9$ ,  $-3.0 \pm 4.3$ ,  $-2.3 \pm 6.4$  cm for satavaptan 5, 12.5, 25 mg/day, respectively compared with  $1.4 \pm 5.9$  cm,  $p < 0.05$  for placebo). The composite end point of ascites worsening was defined as the need for therapeutic intervention or weight gain of 2 kg or more during the study period. A total of 40 patients met this end point, of which 28 had weight gain, ten had an increase in diuretic dose and one underwent paracentesis. A larger percentage of patients with ascites worsened in the placebo group compared with satavaptan groups (placebo: 15/28 [54%], 5 mg/day: 11/28 [39%], 12.5 mg/day: 8/26 [32%] and 25 mg/day: 6/28 [21%]). The difference reached statistical significance for the 25-mg/day group compared with placebo ( $p = 0.026$ ).

In addition, a greater percentage of patients in the satavaptan groups showed improvement of serum  $\text{Na}^+$  concentration at day 5 (or at discharge if sooner) compared with the placebo group. That was defined as an increase in serum  $\text{Na}^+$  concentration of 5 mmol/l or more compared with baseline or serum  $\text{Na}^+$  concentration of 135 mmol/l or more (placebo: 5/28 [18%], 5 mg/day: 17/28 [61%], 12.5 mg/day: 14/26 [54%] and 25 mg/day: 18/28 [64%] ( $p < 0.02$  for all satavaptan groups versus placebo). Similarly, the responders at the end of the treatment period (day 14) were seven out of 28 (26%), 14 out of 28 (50%), 14 out of 26 (54%) and 23 out of 28 (82%), for placebo, satavaptan 5, 12.5 and 25 mg/day, respectively. Moreover, satavaptan groups had a shorter

median time to improvement in serum  $\text{Na}^+$  concentration: 1 day in the 25-mg group and 2 days in the 5- and 12.5-mg groups. Changes in serum osmolality paralleled changes in serum  $\text{Na}^+$  concentration.

The effect on urine volume was recorded. All satavaptan groups showed a greater mean change in urine volume compared with placebo (placebo:  $-56 \pm 739$  ml/day; 5 mg/day:  $756 \pm 770$  ml/day [ $p = 0.06$ ]; 12.5 mg/day:  $1644 \pm 2183$  ml/day; 25 mg/day:  $989 \pm 1470$  ml/day [ $p < 0.001$  for both groups]). Serum creatinine, glomerular filtration rate assessed by modification of diet in renal disease [38], serum  $\text{K}^+$  and urinary  $\text{K}^+$  excretion remained unchanged throughout the study period. However, the urinary  $\text{Na}^+$  excretion increased significantly in the 12.5-mg/day group (placebo: 4 mmol/day; 5 mg/day: 1 mmol/day; 12.5 mg/day: 34 mmol/day [ $p < 0.05$ ]; 25 mg/day: 7 mmol/day).

Satavaptan groups did not have any significant changes in systolic and diastolic blood pressure, heart rate and the activity of the rennin-angiotensin-aldosterone system. There was an increase in serum vasopressin that paralleled the dose of satavaptan.

Treatment-emergent adverse events (TEAEs) were reported with similar frequency in the placebo group compared with the satavaptan 5-, 12.5- and 25-mg groups (TEAEs: 17 [61%], 14 [50%], 14 [54%] and 16 patients [57%], respectively; serious TEAEs: five [18%], four [14%], four [15%] and five patients [18%], respectively). Thirst was the only side effect that was significantly more frequent in patients treated with satavaptan. None of the patients who had rapid correction of serum  $\text{Na}^+$  concentration developed neurologic symptoms. There was a low frequency of hypernatremia, which could be explained by the fact that patients were allowed free access to water. Moreover, satavaptan had showed no effect on hemodynamic parameters (TABLE 3 summarizes TEAEs).

In the second study [37], 176 patients with evidence of cirrhosis, moderate or tense ascites and serum  $\text{Na}^+$  over 130 mmol/l entered a 5–7-day screening period and received daily doses of spironolactone 100 mg and furosemide 20–25 mg. After screening, 28 patients were excluded for different reasons and the remaining 148 patients were enrolled in a 14-day study comparing three fixed daily doses of satavaptan, 5 mg (40 patients), 12.5 mg (35 patients) and 25 mg (38 patients) versus placebo (35 patients). A total of 137 patients completed the study.



**Table 3. Frequency of adverse events and side effects in cirrhotic patients treated with satavaptan versus placebo.**

Side effects and adverse events	Placebo (n = 28)	Satavaptan		
		5 mg/day (n = 28)	12.5 mg/day (n = 26)	25 mg/day (n = 28)
Thirst	1 (4%)	1 (4%)	2 (8%)	8 (29%)
Hypernatremia (serum Na <sup>+</sup> concentration $\geq$ 145 mmol/l)			1	1
Rapid increase in serum Na <sup>+</sup> concentration ( $\geq$ 8 mmol/l in 24 h)**	4	2	3	4
Complications of cirrhosis	3	2	5	5

<sup>†</sup>No neurologic symptoms.  
<sup>‡</sup>Occurred during the first 5 days of therapy.  
 Data taken from [36].

The primary efficacy end point was a change in bodyweight from day 1 to the end of study period (day 14). Satavaptan was associated with a significant reduction of bodyweight compared with placebo. Mean changes in bodyweight from baseline to day 14 for the placebo and satavaptan 5-, 12.5- and 25-mg/day groups were:  $-0.36 \pm 3.03$ ,  $-2.46 \pm 3.11$ ,  $-2.08 \pm 4.17$  and  $-2.28 \pm 3.24$  kg, respectively ( $p = 0.036$ ,  $p = 0.041$  and  $p = 0.036$  for satavaptan 5, 12.5 and 25 mg/day, respectively, compared with placebo).

For the secondary end points the satavaptan groups experienced less abdominal discomfort as measured by a visual analogue compared with placebo ( $-10.7 \pm 31$ ,  $-6.0 \pm 39$  and  $-6.3 \pm 25$  in 5, 12.5 and 25 mg/day, respectively, versus  $1.7 \pm 29$  in the placebo group) and the percentage of patients with ascites worsening was higher in the placebo group (28.6%), compared with the groups treated with satavaptan 5, 12.5 and 25 mg/day (10.5, 17.1 and 10.5%, respectively), although the differences did not reach statistical significance.

The percentage of patients with a weight loss of 2 kg or more at day 14 was greater in the satavaptan groups (55.3, 45.7 and 44.7%,

in patients treated with 5, 12.5 and 25 mg/day, respectively), compared with placebo (28.6%), although the difference was only statistically significant for the 5 mg/day group ( $p = 0.033$ ).

In addition, satavaptan caused a dose-dependent increase in urine volume that occurred after the first dose and was maintained through the study period.

Regarding the effect on serum electrolytes, only the satavaptan 25 mg group caused a statistically significant increase in serum Na<sup>+</sup>. No significant changes were observed in serum creatinine, glomerular filtration rate, urinary Na<sup>+</sup> and potassium excretion, heart rate and arterial pressure. Plasma AVP increased significantly in parallel to the dose of satavaptan, and plasma renin significantly increased in the 12.5- and 25-mg groups.

Treatment-emergent adverse events were examined (TABLE 4): satavaptan groups 5, 12.5 and 25 mg had TEAEs in 21 (52.5%), 18 (51.4%) and 22 (57.9%) patients, respectively, compared with 13 (37.1%) patients in the placebo group.

Serious TEAEs were reported with a similar frequency in the placebo group compared with the satavaptan 5-, 12.5- and 25-mg groups

**Table 4. Frequency of adverse events and side effects in cirrhotic patients treated with satavaptan versus placebo.**

Side effects and adverse events	Placebo (n = 35)	Satavaptan		
		5 mg/day (n = 40)	12.5 mg/day (n = 35)	25 mg/day (n = 38)
Thirst	2 (5.7%)	6 (15%)	10 (28.6%)	10 (26.3%)
Hypernatremia (serum Na <sup>+</sup> concentration $\geq$ 145 mmol/l)	1 (3.2%)	5 (12.5%)	5 (19.2%)	9 (27.3%)
Rapid increase in serum Na <sup>+</sup> concentration ( $\geq$ 8 mmol/l in 24 h)**	2		2	4
Renal impairment (increase in serum creatinine >50% from baseline)	2 (5.7%)	2 (5%)	1 (2.9%)	1 (2.6%)
Complications of cirrhosis	3	1	2	

<sup>†</sup>No neurologic symptoms.  
<sup>‡</sup>Occurred during the first 2 days of therapy.  
 Data taken from [37].

(four [11.4%], four [10%], three [8.6%] and three patients [7.9%], respectively). Thirst was more common in the satavaptan groups compared with placebo (placebo: two [5.7%]; 5 mg: six [15%]; 12.5 mg: ten [28.6%]; 25 mg: ten [26.3%] patients). Hyponatremia occurred in one patient treated with placebo (3.2%), five (12.5%) patients treated with satavaptan 5 mg/day, five (19.2%) patients treated with 12.5 mg/day and nine (27.3%) patients treated with 25 mg/day, and it was related to pretreatment plasma Na<sup>+</sup> level. None of the patients who had rapid correction of serum Na<sup>+</sup> developed neurologic symptoms.

In summary, this study showed similarly efficacy in reducing bodyweight with the three doses of 5, 12.5 and 25 mg with the best safety/efficacy ratio noted with the 5-mg dose.

**Role of satavaptan in heart failure**

Satavaptan has been studied in a heart failure model in rats. Bishara *et al.* showed that acute treatment with satavaptan caused significant diuresis and reduced U<sub>osm</sub> [39]. Chronic treatment for 28 days increased urine volume two- to five-fold throughout the study period and caused a reduction in heart weight and an improvement in cardiac hypertrophy. This effect on cardiac remodeling is speculated to be secondary to the improvement in the hemodynamic status in heart failure rats by reducing preload due to its potent diuretic effect. In addition, satavaptan decreased the heart weight/body weight ratio by abolishing weight gain in the treated

rats compared with the control group. By contrast, Van Kerckhoven *et al.* showed no effect of 21-day treatment with satavaptan on cardiac hypertrophy in rats with heart failure induced by ligation of coronary arteries (TABLE 5) [40]. These results warrant further studies to evaluate this potential use of satavaptan.

**Role of satavaptan in the treatment of autosomal dominant polycystic kidney disease**

V2 receptors are mainly expressed in the renal collecting ducts and activation of these receptors results in marked proliferation of renal epithelial cells in autosomal dominant polycystic kidney disease [41,42]. V2 receptor antagonists have shown potential to prevent the progression of this disease [43,44]. To examine the potential effect of satavaptan on halting cellular growth, Bolignano *et al.* tested increasing doses of satavaptan on cell apoptosis in V2-R<sup>+</sup> renal tubular line Lilly Laboratories Cell–Porcine Kidney (LLC–PK1) and V2-R<sup>-</sup> ovarian Chinese Hamster (CHO) line [45]. Satavaptan caused dose-dependent increase in apoptosis percentage. This study should encourage more research on the potential use of satavaptan in the treatment of autosomal dominant polycystic kidney disease.

**Role of satavaptan in renal cell cancer treatment**

There is recent evidence that different types of cancer cells express AVP receptors [46–48]. For example, breast cancer cells overexpress

Table 5. Effects of satavaptan in animal models of heart failure.

Study	Species	Condition of species	Intervention	Results	Ref.
Bishara <i>et al.</i>	Rats (male Sprague-Dawley)	CHF induced by arterio-venous fistula	Acute studies: • 0.3 mg/kg iv. SR121463B Chronic studies: • ip. 3 mg/kg/day SR121463B for 7 and 28 days or oral 3 mg/kg/day SR121463B for 7 days	Acute studies: • SR121463B increased U <sub>v</sub> and reduced U <sub>osm</sub> without significant natriuretic effect or reduction in MAP in both control and CHF rats Chronic studies: • Oral and ip. SR121463B for 7 days produced significant increase in cumulative U <sub>v</sub> . Only oral SR121463B caused decrease in U <sub>osm</sub> - 7 days of SR121463B did not affect cardiac hypertrophy - 28-day treatment with SR121463B reduced heart weight	[39]
Van Kerckhoven <i>et al.</i>	Rats (male Wistar)	MI induced by ligating the left anterior descending artery	sc. SR121463B for 21 days	Did not improve cardiac output, stroke volume or cardiac remodeling. No effect on MAP, pre- and post-load	[40]

CHF: Congestive heart failure; ip.: Intraperitoneal; iv.: Intravenous; MAP: Mean arterial pressure; MI: Myocardial infarction; sc. Subcutaneous; U<sub>osm</sub>: Urine osmolality; U<sub>v</sub>: Urine volume.

V1A receptor and applying a V1A receptor antagonist inhibits the mitogenic effect of pro-AVP [49]. Since the V2 receptor is mainly expressed on the surface of renal collecting ducts; it is unclear whether AVP and V2 receptor blockade have an effect on renal cell cancer growth. Bolignano *et al.* demonstrated that CAKI-2 and A498 cell lines, derived from primary clear cell renal carcinoma from male and female patients, express V2 receptors [50]. In addition, he found that DDAVP stimulates cellular proliferation in both cell lines. This growth was completely prevented by the addition of satavaptan 1 nM. This opens new therapeutic potentials for the use of satavaptan in the treatment of various types of cancer. A validation of this therapeutic potential of satavaptan is needed in *in vivo* models.

### Role of satavaptan in glaucoma

Glaucoma is a group of diseases characterized by a progressive damage of the optic nerve leading to impairment of the visual field. Elevated intraocular pressure (IOP) represents a major risk factor for glaucoma. Different mechanisms regulate the IOP, including: the rate of aqueous humor secretion; the outflow through the trabecular meshwork; the uveoscleral outflow; and the episcleral venous pressure.

Most of the treatments that are available for glaucoma are directed towards lowering the IOP.  $\beta$ -adrenergic antagonists and carbonic anhydrase inhibitors decrease the aqueous humor production. Cholinergic agonists increase the trabecular meshwork outflow. Prostaglandin analogs increase the uveoscleral outflow and  $\alpha$ -adrenergic agonists have mixed effects. However, none of these treatments are satisfactory in terms of duration of action, absence of tachyphylaxis, easy administration or tolerance, hence the search for different treatments continues.

As vasopressin-like peptides were found in the rabbit anterior uvea, Lacheretz *et al.* designed a study to assess a possible effect of selective V2 receptor antagonist (satavaptan) on IOP in an animal model of glaucoma [51].

In their study, they demonstrated that satavaptan induced a significant decrease in IOP after instillation in the hypertensive eye in an animal model of ocular hypertension. The duration of action was 6–8 h, and the effect was maintained after repeated instillations with no contralateral IOP changes in the other eye or systemic effects. When the drug was applied on a normotensive eye, no effect was noticed.

After systemic administration, satavaptan had the same lowering effect of IOP of the hypertensive eye without affecting the pressure on the normotensive one.

Since V2 receptors have not been found in eye structures, the activity of satavaptan remains unexplained. Further studies should be carried out before this drug becomes commercially available to treat glaucoma.

### Role of satavaptan in diabetic nephropathy

In patients with Type 1 and 2 diabetes mellitus, AVP levels are elevated [52]. This is also documented in rats with induced or genetic diabetes mellitus [53,54]. This elevation in AVP is believed to play a role in diabetes-induced albuminuria through interaction with V2 receptors in rats and humans [55–57], hence the potential use of V2 receptor antagonists to help prevent diabetic nephropathy. In a study by Bardoux *et al.*, chronic satavaptan treatment has been shown to prevent the elevation of urinary albumin excretion in rats with induced diabetes compared with a control group without treatment [58]. This potential use of V2 receptor antagonists deserves more evaluation in humans.

### Effect of satavaptan on renal immune response & antibacterial defense

Pyelonephritis is a very common infection and usually caused by Gram-negative bacteria. Collecting duct cells are the preferential intrarenal site of bacterial adhesion and initiation of inflammatory response. Toll-like receptor 4, which recognizes lipopolysaccharides (LPSs), constituents of the outer membrane of Gram-negative bacteria, plays a central role in initiating the antibacterial host response via activation of the nuclear transcription factor NF- $\kappa$ B signaling pathway and the subsequent production of chemokines and cytokines [59].

Previous studies have shown that increased cell cAMP levels inhibit the TNF- $\alpha$ -, LPS- and IL-1 $\beta$ -stimulated expression of adhesion molecules and signaling molecules in a variety of cell types [60–63]. AVP, via its stimulatory action on cell cAMP content, might therefore inhibit the activation of collecting duct cells after bacterial colonization of the kidney. This was confirmed by Chassin *et al.*, who showed that the pure V2R agonist dDAVP induced a dose-dependent decrease of the LPS-induced activation of NF- $\kappa$ B, macrophage inflammatory protein 2 (MIP-2) and TNF- $\alpha$  *in vitro*

and *in vivo* [64]. SR121463B produced concentration-dependent antagonism of the inhibitory action of dDAVP on LPS-induced MIP-2 secretion. Therefore, this study supports the use of satavaptan in pyelonephritis: firstly, by stimulating the expression of proinflammatory mediators to kill the uropathogenic *Escherichia coli* colonizing the kidneys and, secondly, by the aquaretic effect, blocking retrograde bacteria ascent by mechanic dilution. Thus, this study shows for the first time an immune role of V2R involved in antibacterial host defense playing a key role in urinary infections.

### Regulatory status of satavaptan

On 23 May 2008, Sanofi-Aventis officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorization for satavaptan (Aquilda®), for the treatment of euvolemic and hypovolemic dilutional hyponatremia based on the request of the CHMP for additional information on the therapeutic safety and efficacy of satavaptan. The main concern of the CHMP was related to the effectiveness of the medicine, since there were too few patients treated and they were not treated for long enough. The CHMP noted that all of the studies looked at the effect of satavaptan on

blood Na<sup>+</sup> levels, and did not look at its effect on measures that are more relevant to patients, such as the improvement in symptoms. The CHMP also noted that correcting Na<sup>+</sup> levels in patients with hypovolemic hyponatremia is of limited benefit unless it helps to treat the underlying liver or heart disease [101].

### Conclusion

Satavaptan is a selective V2 receptor antagonist that appears promising the treatment of hyponatremia and cirrhotic ascites. In addition, its potential use for other conditions such as polycystic kidney disease, renal cell carcinoma, glaucoma, diabetic nephropathy and pyelonephritis needs further exploration.

### Financial & competing interests disclosure

*The contents are solely the responsibility of the authors and do not represent the official view of any organizations. Dr Ghali is a Consultant and has received research grants and honoraria from Otsuka, Astellas, Cardiokine Inc. and Biogen Idec. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

*No writing assistance was utilized in the production of this manuscript.*

### Executive summary

#### Arginine vasopressin hormone

- Arginine vasopressin hormone (AVP) plays a major role in plasma Na<sup>+</sup> regulation.
- Its secretion is controlled by changes in plasma osmolality, status of volume and angiotensin II.
- AVP stimulation of V2 receptors allows water reabsorption through aquaporin 2 channels in renal collecting duct cells.

#### Satavaptan (SR121463)

- Is an orally active, nonpeptide antagonist of AVP V2 receptors that has been shown to do the following:
  - Preclinical studies:
    - Induces a dose-dependent increase in urine flow rate (water clearance), and a decrease in urine osmolality without significant change in urinary Na<sup>+</sup> and K<sup>+</sup> excretion in normal rats and in hyponatremic cirrhotic rats.
    - Possible but not confirmed beneficial effect on cardiac hypertrophy in rat models with heart failure.
    - Dose-dependent increase in apoptosis in renal tubule cells carrying V2 receptors, suggesting a potential for use in autosomal dominant polycystic kidney disease.
    - Inhibits clear renal cell carcinoma growth *in vivo*.
    - Induces a significant decrease in intraocular pressure after topical and systemic administration in a rat model of ocular hypertension without affecting normotensive eye.
    - Prevents the increase of urinary albumin excretion in rats with induced diabetes.
    - It normalizes serum Na<sup>+</sup> in hyponatremia cirrhotic rats.
    - Potential use in pyelonephritis through stimulating proinflammatory mediators to kill bacteria colonizing the kidneys and by blocking retrograde bacteria ascent by mechanic dilution.
  - Clinical studies:
    - Corrects hyponatremia in patients with syndrome of inappropriate antidiuretic hormone secretion and cirrhosis.
    - A promising effect in the treatment of cirrhotic ascites.
  - Medication marketing status:
    - The application for marketing satavaptan for the treatment of euvolemic and hypovolemic hyponatremia was withdrawn based on a request from the Committee for Medicinal Products for Human Use for additional information on the therapeutic safety and efficacy of satavaptan.

## Bibliography

Papers of special note have been highlighted as:

■ of interest

■ ■ of considerable interest

- 1 Ghali JK: Mechanisms, risks, and new treatment options for hyponatremia. *Cardiology* 111(3), 147–157 (2008).
- 2 Boscoe A, Paramore C, Verbalis JG: Cost of illness of hyponatremia in the United States. *Cost Eff. Resour. Alloc.* 4, 10 (2006).
- 3 Shea AM, Hammill BG, Curtis LH, Szczech LA, Schulman KA: Medical costs of abnormal serum sodium levels. *J. Am. Soc. Nephrol.* 19(4), 764–770 (2008).
- 4 Zilberberg MD, Exuzides A, Spalding J *et al.*: Epidemiology, clinical and economic outcomes of admission hyponatremia among hospitalized patients. *Curr. Med. Res. Opin.* 24(6), 1601–1608 (2008).
- 5 Wade CE, Keil LC, Ramsay DJ: Role of volume and osmolality in the control of plasma vasopressin in dehydrated dogs. *Neuroendocrinology* 37(5), 349–353 (1983).
- 6 Bourque CW, Oliet SH: Osmoreceptors in the central nervous system. *Annu. Rev. Physiol.* 59, 601–619 (1997).
- 7 Oliet SH, Bourque CW: Mechanosensitive channels transduce osmosensitivity in supraoptic neurons. *Nature* 364(6435), 341–343 (1993).
- 8 Schrier RW: Water and sodium retention in edematous disorders: role of vasopressin and aldosterone. *Am. J. Med.* 119(7 Suppl. 1), S47–S53 (2006).
- 9 Mitchell LD, Barron K, Brody MJ, Johnson AK: Two possible actions for circulating angiotensin II in the control of vasopressin release. *Peptides* 3(3), 503–507 (1982).
- 10 Brooks VL, Keil LC, Reid IA: Role of the renin–angiotensin system in the control of vasopressin secretion in conscious dogs. *Circ. Res.* 58(6), 829–838 (1986).
- 11 Thibonnier M, Conarty DM, Preston JA, Wilkins PL, Berti-Mattera LN, Mattera R: Molecular pharmacology of human vasopressin receptors. *Adv. Exp. Med. Biol.* 449, 251–276 (1998).
- 12 Ghali JK, Farah JO, Daifallah S, Zabalawi HA, Zmily HD: Conivaptan and its role in the treatment of hyponatremia. *Drug Des. Devel. Ther.* 3, 253–268 (2009).
- 13 Young WS, Li J, Wersinger SR, Palkovits M: The vasopressin 1b receptor is prominent in the hippocampal area CA2 where it is unaffected by restraint stress or adrenalectomy. *Neuroscience* 143(4), 1031–1039 (2006).
- 14 Antoni FA: Vasopressinergic control of pituitary adrenocorticotropin secretion comes of age. *Front. Neuroendocrinol.* 14(2), 76–122 (1993).
- 15 Tanoue A, Ito S, Honda K *et al.*: The vasopressin V1b receptor critically regulates hypothalamic–pituitary–adrenal axis activity under both stress and resting conditions. *J. Clin. Invest.* 113(2), 302–309 (2004).
- 16 Ali F, Guglin M, Vaitkevicius P, Ghali JK: Therapeutic potential of vasopressin receptor antagonists. *Drugs* 67(6), 847–858 (2007).
- 17 Mayinger B, Hensen J: Nonpeptide vasopressin antagonists: a new group of hormone blockers entering the scene. *Exp. Clin. Endocrinol. Diabetes* 107(3), 157–165 (1999).
- 18 Serradeil-Le Gal C, Lacour C, Valette G *et al.*: Characterization of SR 121463A, a highly potent and selective, orally active vasopressin V2 receptor antagonist. *J. Clin. Invest.* 98(12), 2729–2738 (1996).
- ■ **One of the first papers to describe satavaptan and its effects.**
- 19 Serradeil-Le Gal C, Raufaste D, Double-Cazanave E *et al.*: Binding properties of a selective tritiated vasopressin V2 receptor antagonist, [H]-SR 121463. *Kidney Int.* 58(4), 1613–1622 (2000).
- ■ **One of the first papers to describe satavaptan and its effects.**
- 20 Serradeil-Le Gal C: An overview of SR121463, a selective non-peptide vasopressin V(2) receptor antagonist. *Cardiovasc. Drug Rev.* 19(3), 201–214 (2001).
- ■ **One of the first papers to describe satavaptan and its effects.**
- 21 Bernat A, Hoffmann P, Dumas A, Serradeil-Le Gal C, Raufaste D, Herbert JM: V2 receptor antagonism of DDAVP-induced release of hemostasis factors in conscious dogs. *J. Pharmacol. Exp. Ther.* 282(2), 597–602 (1997).
- ■ **Multicenter, double-blind, placebo-controlled study of satavaptan in humans with hyponatremia.**
- 22 Soupert A, Gross P, Legros JJ *et al.*: Successful long-term treatment of hyponatremia in syndrome of inappropriate antidiuretic hormone secretion with satavaptan (SR121463B), an orally active nonpeptide vasopressin V2-receptor antagonist. *Clin. J. Am. Soc. Nephrol.* 1(6), 1154–1160 (2006).
- 23 Shen T, Laycock J, Suzuki Y, Defer N, Hanoune J: Stability of the vasopressin V2 receptor-adenylyl cyclase system in rat kidney. *Eur. J. Pharmacol.* 341(1), 87–94 (1998).
- 24 Huang DY, Pfaff I, Serradeil-Le Gal C, Vallon V: Acute renal response to the non-peptide vasopressin V2-receptor antagonist SR 121463B in anesthetized rats. *Naunyn Schmiedebergs Arch. Pharmacol.* 362(3), 201–207 (2000).
- 25 Promeneur D, Kwon TH, Frokiaer J, Knepper MA, Nielsen S: Vasopressin V(2)-receptor-dependent regulation of AQP2 expression in Brattleboro rats. *Am. J. Physiol. Renal Physiol.* 279(2), F370–F382 (2000).
- 26 Lacour C, Galindo G, Canals F *et al.*: Aquaretic and hormonal effects of a vasopressin V(2) receptor antagonist after acute and long-term treatment in rats. *Eur. J. Pharmacol.* 394(1), 131–138 (2000).
- 27 Pouzet B, Serradeil-Le Gal C, Bouby N, Maffrand JP, Le Fur G, Bankir L: Selective blockade of vasopressin V2 receptors reveals significant V2-mediated water reabsorption in Brattleboro rats with diabetes insipidus. *Nephrol. Dial. Transplant.* 16(4), 725–734 (2001).
- 28 Yao L, Huang DY, Pfaff IL, Nie X, Leitges M, Vallon V: Evidence for a role of protein kinase c- $\alpha$  in urine concentration. *Am. J. Physiol. Renal Physiol.* 287(2), F299–F304 (2004).
- 29 Robertson GL, Shelton RL, Athar S: The osmoregulation of vasopressin. *Kidney Int.* 10(1), 25–37 (1976).
- 30 Perucca J, Bichet DG, Bardoux P, Bouby N, Bankir L: Sodium excretion in response to vasopressin and selective vasopressin receptor antagonists. *J. Am. Soc. Nephrol.* 19(9), 1721–1731 (2008).
- 31 Yamamura Y, Nakamura S, Itoh S *et al.*: OPC-41061, a highly potent human vasopressin V2-receptor antagonist: pharmacological profile and aquaretic effect by single and multiple oral dosing in rats. *J. Pharmacol. Exp. Ther.* 287(3), 860–867 (1998).
- 32 Jimenez W, Gal CS, Ros J *et al.*: Long-term aquaretic efficacy of a selective nonpeptide V(2)-vasopressin receptor antagonist, SR121463, in cirrhotic rats. *J. Pharmacol. Exp. Ther.* 295(1), 83–90 (2000).
- 33 Gerbes AL, Gulberg V, Gines P *et al.*: Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: a randomized double-blind multicenter trial. *Gastroenterology* 124(4), 933–939 (2003).
- 34 Wong F, Blei AT, Blendis LM, Thuluvath PJ: A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: a multicenter, randomized, placebo-controlled trial. *Hepatology* 37(1), 182–191 (2003).
- 35 Schrier RW, Gross P, Gheorghiadu M *et al.*: Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N. Engl. J. Med.* 355(20), 2099–2112 (2006).



- 36 Gines P, Wong F, Watson H, Milutinovic S, Del Arbol LR, Olteanu D: Effects of satavaptan, a selective vasopressin V(2) receptor antagonist, on ascites and serum sodium in cirrhosis with hyponatremia: a randomized trial. *Hepatology* 48(1), 204–213 (2008).
- **A multicenter, double-blind, placebo-controlled trial of satavaptan in humans with cirrhosis with and without hyponatremia.**
- 37 Gines P, Wong F, Watson H, Terg R, Bruha R, Zarski JP: Clinical trial: short-term effects of combination of satavaptan, a selective vasopressin V receptor antagonist, and diuretics on ascites in patients with cirrhosis without hyponatremia – a randomized, double-blind, placebo-controlled study. *Aliment. Pharmacol. Ther.* 31(8), 834–845 (2010).
- **A multicenter, double-blind, placebo-controlled trial of satavaptan in humans with cirrhosis with and without hyponatremia.**
- 38 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. *Ann. Intern. Med.* 130(6), 461–470 (1999).
- 39 Bishara B, Shiekh H, Karram T *et al.*: Effects of novel vasopressin receptor antagonists on renal function and cardiac hypertrophy in rats with experimental congestive heart failure. *J. Pharmacol. Exp. Ther.* 326(2), 414–422 (2008).
- **Describes animal models with congestive heart failure (CHF) and the effect of satavaptan.**
- 40 Van Kerckhoven R, Lankhuizen I, Van Veghel R, Saxena PR, Schoemaker RG: Chronic vasopressin V(1A) but not V(2) receptor antagonism prevents heart failure in chronically infarcted rats. *Eur. J. Pharmacol.* 449(1–2), 135–141 (2002).
- **Describes animal models with CHF and the effect of satavaptan.**
- 41 Yamaguchi T, Pelling JC, Ramaswamy NT *et al.*: Camp stimulates the *in vitro* proliferation of renal cyst epithelial cells by activating the extracellular signal-regulated kinase pathway. *Kidney Int.* 57(4), 1460–1471 (2000).
- 42 Belibi FA, Reif G, Wallace DP *et al.*: Cyclic AMP promotes growth and secretion in human polycystic kidney epithelial cells. *Kidney Int.* 66(3), 964–973 (2004).
- 43 Gattone VH 2nd, Wang X, Harris PC, Torres VE: Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. *Nat. Med.* 9(10), 1323–1326 (2003).
- 44 Torres VE, Wang X, Qian Q, Somlo S, Harris PC, Gattone VH 2nd: Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease. *Nat. Med.* 10(4), 363–364 (2004).
- 45 Bolignano D, Medici MA, Buemi M: Aquaretic-induced apoptosis: a cure or a curse? *Eur. J. Clin. Invest.* 38(11), 874–875 (2008).
- **Demonstrates the potential of v2 receptors in fighting urinary tract infection.**
- 46 North WG, Fay MJ, Du J: MCF-7 breast cancer cells express normal forms of all vasopressin receptors plus an abnormal V2R. *Peptides* 20(7), 837–842 (1999).
- 47 North WG: Gene regulation of vasopressin and vasopressin receptors in cancer. *Exp. Physiol.* 85 Spec No, 27S–40S (2000).
- 48 Treschan TA, Peters J: The vasopressin system: physiology and clinical strategies. *Anesthesiology* 105(3), 599–612; quiz 639–640 (2006).
- 49 Keegan BP, Akerman BL, Pequeux C, North WG: Provasopressin expression by breast cancer cells: implications for growth and novel treatment strategies. *Breast Cancer Res. Treat.* 95(3), 265–277 (2006).
- 50 Bolignano D, Medici MA, Coppolino G *et al.*: Aquaretic inhibits renal cancer proliferation: role of vasopressin receptor-2 (V2-R). *Urol. Oncol.* (2009) (Epub ahead of print).
- **Demonstrated the potential of v2 receptors in fighting urinary tract infection.**
- 51 Lacheretz F, Barbier A, Serradeil-Le Gal C, Elena PP, Maffrand JP, Le Fur G: Effect of SR121463, a selective non-peptide vasopressin V2 receptor antagonist, in a rabbit model of ocular hypertension. *J. Ocul. Pharmacol. Ther.* 16(3), 203–216 (2000).
- 52 Davis FB, Davis PJ: Water metabolism in diabetes mellitus. *Am. J. Med.* 70(1), 210–214 (1981).
- 53 Zerbe RL, Vinicor F, Robertson GL: Plasma vasopressin in uncontrolled diabetes mellitus. *Diabetes* 28(5), 503–508 (1979).
- 54 Bankir L, Bardoux P, Ahloulay M: Vasopressin and diabetes mellitus. *Nephron* 87(1), 8–18 (2001).
- 55 Bouby N, Bachmann S, Bichet D, Bankir L: Effect of water intake on the progression of chronic renal failure in the 5/6 nephrectomized rat. *Am. J. Physiol.* 258(4 Pt 2), F973–F979 (1990).
- 56 Bouby N, Hassler C, Bankir L: Contribution of vasopressin to progression of chronic renal failure: study in Brattleboro rats. *Life Sci.* 65(10), 991–1004 (1999).
- 57 Bardoux P, Bichet DG, Martin H *et al.*: Vasopressin increases urinary albumin excretion in rats and humans: involvement of V2 receptors and the renin–angiotensin system. *Nephrol. Dial. Transplant.* 18(3), 497–506 (2003).
- 58 Bardoux P, Bruneval P, Heudes D, Bouby N, Bankir L: Diabetes-induced albuminuria: role of antidiuretic hormone as revealed by chronic V2 receptor antagonism in rats. *Nephrol. Dial. Transplant.* 18(9), 1755–1763 (2003).
- 59 Zhang G, Ghosh S: Toll-like receptor-mediated NF- $\kappa$ B activation: a phylogenetically conserved paradigm in innate immunity. *J. Clin. Invest.* 107(1), 13–19 (2001).
- 60 Panettieri RA Jr, Lazaar AL, Pure E, Albelda SM: Activation of cAMP-dependent pathways in human airway smooth muscle cells inhibits TNF- $\alpha$ -induced ICAM-1 and VCAM-1 expression and T lymphocyte adhesion. *J. Immunol.* 154(5), 2358–2365 (1995).
- 61 Feng WG, Wang YB, Zhang JS, Wang XY, Li CL, Chang ZL: cAMP elevators inhibit LPS-induced IL-12 p40 expression by interfering with phosphorylation of p38 MAPK in murine peritoneal macrophages. *Cell Res.* 12(5–6), 331–337 (2002).
- 62 Osawa Y, Lee HT, Hirshman CA, Xu D, Emala CW: Lipopolysaccharide-induced sensitization of adenylyl cyclase activity in murine macrophages. *Am. J. Physiol. Cell Physiol.* 290(1), C143–C151 (2006).
- 63 Aronoff DM, Canetti C, Serezani CH, Luo M, Peters-Golden M: Cutting edge: macrophage inhibition by cyclic AMP (cAMP): differential roles of protein kinase A and exchange protein directly activated by cAMP-1. *J. Immunol.* 174(2), 595–599 (2005).
- 64 Chassin C, Hornef MW, Bens M *et al.*: Hormonal control of the renal immune response and antibacterial host defense by arginine vasopressin. *J. Exp. Med.* 204(12), 2837–2852 (2007).
- **Demonstrates the potential of v2 receptors in fighting urinary tract infection.**

## ■ Website

- 101 European Medicines Agency, London, UK  
www.ema.europa.eu