Editorial

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May vaptans contribute to the treatment of refractory ascites?

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Ascites is one of the most frequent complications of cirrhosis. Indeed, ascites develops in about 50% of cirrhotic patients and in many of them it will become refractory ascites, which is defined as an ascites that cannot be mobilized by the standard therapy with dietary salt restriction and with diuretic medications at doses of up to 160 mg/day of furosemide and 400 mg/day of spironolactone [1].

The quality of life of patients with refractory ascites progressively deteriorates. Their risk in developing other portal hypertension-related complications is high, and their probability of survival is strongly reduced.

Liver transplantation is the only treatment which allows for bypassing these problems; however, only a small subgroup of patients with refractory ascites ever has the chance to be successfully transplanted.

In most patients refractory ascites is treated conservatively. The main goal of treatment is to relieve tense ascites, to prevent further complications such as renal failure, encephalopathy, cramps, and herniations, and to prolong survival so that the chances for receiving liver transplantion are improved.

To date, the standard treatment for refractory ascites is repeated large-volume paracentesis (LVP) combined with an i.v. infusion of albumin [2]. LVP has been shown to have less side effects than diuretic treatment [3] and is at least as effective as a LeVeen shunt, a treatment that has almost been completely abandoned due to the high rate of malfunction or obstruction of the shunt [4]. LVP allows for rapid relief of the abdominal tension created by ascites. However, since LVP does not correct the mechanisms causing ascites, ascites re-accumulates and paracentesis must be repeated after a variable period of time. Some patients that have a very low capacity to excrete sodium, re-accumulate ascites so rapidly that paracentesis must be repeated every few days, which is very inconvenient for the patient. Alternatively, the insertion of a transjugular intrahepatic portosystemic stent shunt (TIPS), which reduces portal pressure, has been demonstrated to be able to reduce ascites formation, avoid paracentesis, and, in well-selected patients, improve survival [5]. Accordingly, some consider TIPS as the first option for the treatment of patients with refractory ascites. However, many cirrhotic patients with refractory ascites cannot be treated with TIPS because of contraindications, the most frequent of which are encephalopathy, hyperbilirubinemia, high Child-Pugh score, cardiorespiratory failure, pulmonary hypertension, older age, porto-mesenteric thrombosis, intrahepatic bile ducts dilatation, and polycystic liver disease. For this reason TIPS should be reserved for patients who do not tolerate repeated LVP and who do not show any of the aforementioned contraindications. This group of patients represents more or less 40–50% of cirrhotic patients with refractory ascites [6].

There are no other conservative treatments currently available. Therefore, the possibility of combining diuretics with new drugs resulting in a better control of ascites, without increasing the risk of side-effects, is a relevant issue. An improvement in the effect of diuretic medications could be obtained with the chronic administration of albumin [7] or with vasoconstrictor agents which reduce splanchnic blood flow. Terlipressin must be given intravenously and is too expensive to be used chronically, while midodrine can be given orally, is cheaper, and has been demonstrated to increase urine sodium excretion when given after LVP [8]. However, we need powerful RCTs to confirm the utility of these strategies.

Arginine–vasopressin-receptor antagonists, or vaptans, are a new class of drugs able to increase free water excretion. They work as antagonists of the V2 receptors of vasopressin, which are located in the principal cells of the renal-collecting-duct system. As these receptors regulate the reabsorption of free water, their inhibition increases water excretion causing a reduction in urine osmolality and an increase in plasma osmolality [9]. Therefore, the main indication for giving vaptans is the treatment of euvolemic or hypervolemic hyponatremia caused by an inappropriate release of antidiuretic hormone [10].

Some peptide vasopressin-receptor antagonists have been developed since the 1960s. However, the need for parenteral administration and the unexpected property of an intrinsic agonistic effect, in addition to the antagonistic effects, precluded their widespread or chronic use in patients [11].

By contrast, the new non-peptide vasopressin-receptor antagonists, or vaptans, are orally active and seem to maintain their antagonistic effect also when given chronically.

Many human disorders are associated with hyponatremia. Vaptans have been tested in various clinical disorders with hyponatremia, mainly in acute and chronic cardiac failure [12–13].

Five non-peptide antagonists are now at various stages in randomized controlled trials (RCTs) (Table 1).

Some of them have also been tested in cirrhotic patients with the aim of correcting hyponatremia [11,14], and in some

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Table 1. No-peptide V2-receptor antagonists.

Generic name	Tolvaptan	Lixivaptam	Satavaptan	Mozavaptan	Conivaptan
Administration	Oral	Oral	Oral or iv	Oral	Oral or iv
Dose	15–60 mg	50–100 mg	5–25	30–60	40–80
Selective index (Va1/V2)	29	100	112	10	0–15
Half life (h)	6–8	7–10	14–17		31–78
Metabolism	Hepatic	Hepatic	Hepatic	Hepatic	Hepatic

cases, to reduce oedema. The rationale for the latter indication is that by increasing free water excretion, vaptans can cause a moderate hypovolemia and thus induce oedema reabsorption.

In the present issue of the Journal, Wong et al. [15] report the results of a RCT where three different doses of Satavaptan (5, 12.5, and 25 mg/day) and a placebo were given to hypo- or normo-natremic cirrhotic patients with ascites which periodically required LVP. All subjects also received a small dose of spironolactone (100 mg). The main endpoints of the study were the length of the interval between two consecutive paracentesis and the weekly amount of ascites accumulation estimated by summing up the litres of ascites removed with paracentesis and by following the changes in kilograms of body weight. A secondary end-point was the total number of paracentesis performed during 12 weeks of treatment. The trial was double-blind and was based on the rationale that increasing the urine volume by antagonizing the renal effects of arginine–vasopressin can delay the recurrence of ascites after paracentesis. A possible enhancement of the diuretic power of spironalactone was also possible, since Satavaptan was shown to transiently increase sodium excretion [16].

By a statistical point of view, the main end-points of the study were not achieved, even if the total number of paracentesis performed during the 12 weeks of observation was significantly lower in patients taking Satavaptan.

Thus, these data suggest that the administration of an antagonist of the V2 receptors of arginine–vasopressin to patients with advanced cirrhosis and ascites may produce only a minor effect in the control of ascites. Taking into account that some side-effects frequently occurred in patients treated with Satavaptan, such as orthostatic hypotension, encephalopathy, muscle cramps, and hyperkalemia, the use of Satavaptan could cause more trouble than it is worth.

However, there are a series of issues that deserve to be considered before giving a final evaluation on the effects of Satavaptan in cirrhotic patients with severe ascites.

First, in this study Satavaptan was combined with 100 mg/day of spironolactone, a very small dose for patients with a long-lasting history of ascites (more than one year). Accordingly, we cannot predict what could be the effect of Satavaptan given with higher doses of spironolactone or in association with a combination of spironolactone and furosemide that is the more common therapy in cirrhotic patients with severe (but not refractory) ascites.

Second, the best effects were obtained with the first two doses of Satavaptan (5 and 12.5 mg) and there was not a dose-dependent effect. This brings up the possibility that a dose lower than 5 mg/day could be equally effective and produce less side-effects.

Third, 57 (38%) out of 151 patients did not complete the study; for many this was due to drug intolerance. A similar number of discontinuations may have considerably affected the results.

Lastly, the efficacy and safety of Satavaptan for longer periods of time is still unknown. Obtaining this information will be necessary in order to evaluate the risk/benefit ratio for the chronic use of Satavaptan outside RCTs.

In conclusion, Satavaptan is a potent antagonist of the renal effects of arginine–vasopressin that, in combination with diuretics, could play a role in the treatment of recurrent or refractory ascites, as well as in the correction of hyponatremia. These potentialities make Satavaptan a drug of great interest for cirrhotic patients as well as for patients with other oedemigeneous disorders. However, we need to answer questions that are still unresolved regarding their use. In particular, whereas the ability to correct hyponatremia is a well-proven therapeutic effect, the ability to improve the management of severe ascites should still be tested with further RCTs.

Conflicts of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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