Research Article

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Effects of a selective vasopressin V_2 receptor antagonist, satavaptan, on ascites recurrence after paracentesis in patients with cirrhosis☆

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Background & Aims: Cirrhotic patients with recurrent ascites frequently require paracentesis despite diuretic therapy. Vasopressin receptor antagonists, by increasing free water clearance, may reduce the recurrence of ascites. To investigate the effects of the addition of a vasopressin V_2 receptor antagonist, satavaptan, to 100 mg spironolactone on ascites recurrence after a large volume paracentesis in patients with liver cirrhosis irrespective of the presence of hyponatraemia.

Methods: One hundred and fifty one cirrhotic patients with recurrent ascites with or without hyponatraemia, and normal to mildly abnormal renal function were randomised in a double-blind study to receive either 5 mg ($n = 39$), 12.5 mg ($n = 36$), 25 mg ($n = 40$) of satavaptan or placebo ($n = 36$) for 12 weeks. Their Child–Pugh scores were 9.2 ± 1.3, 8.7 ± 1.7, 8.8 ± 1.3, and 9.0 ± 1.5, respectively.

Results: Median time to first paracentesis was 23, 26, and 17 days with satavaptan 5, 12.5, and 25 mg, respectively, versus 14 days with placebo (ns for all doses). The frequency of paracenteses was decreased significantly ($p < 0.05$) in all satavaptan groups versus placebo. Mean increase in ascites was 2.82 ± 0.48 L/week for placebo versus 2.12 ± 0.40, 2.14 ± 0.33, and 2.06 ± 0.40 L/week for the 5, 12.5, and 25 mg of satavaptan, respectively (ns for all doses). Similar numbers of patients experienced major adverse events in all groups. Increases in serum creatinine, orthostatic changes in systolic pressure and thirst were more common with satavaptan.

Conclusions: Satavaptan has the potential to reduce recurrence of ascites after a large volume paracentesis at doses from 5 to 25 mg in cirrhotic patients with ascites.

Introduction

The development of ascites in the natural history of cirrhosis heralds a worsening of the prognosis to 50% survival at 2 years [1], and this deteriorates to 30–50% at 1 year when the ascites becomes refractory to medical therapy [2,3]. Traditionally, the management of ascites consists of dietary sodium restriction, judicious use of diuretics, and large volume paracentesis (LVP) [4]. Although repeated LVPs have been shown to be safe [5,6], frequent LVPs involve significant medical manpower and inconvenience to the patients. Other treatment options, including the insertion of a transjugular intrahepatic portosystemic stent shunt, are only suitable for carefully selected patients [7].

Vasopressin V_2 receptor antagonists are aquaretic agents. By antagonising the antidiuretic effects of vasopressin at the V_2 receptor located in the renal collecting duct, they increase free water clearance, and thus may be helpful in mobilising excess water in conditions associated with water retention including cirrhosis [8–10]. The use of V_2 receptor antagonists in cirrhosis with ascites has be shown to be safe and efficacious, with a dose-dependent increase in urinary volume and a reduction in urinary osmolality [8,9]. Furthermore, while cirrhotic patients with ascites on placebo gained weight, those on aquaretic agents maintained their weight with the lower doses, and clearly lost weight with the higher doses [8,9].

Satavaptan is a selective V_2 receptor antagonist, which increased urine output when administered with spironolactone in cirrhotic patients with ascites and hyponatraemia [11], associated

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Abbreviations: AST, aspartate transaminase; ALT, alanine transaminases; ALP, alkaline phosphatase; CI, confidence interval; dDAVP, 1-desamino-8-D-arginine vasopressin; INR, international normalized ratio; ITT, intention to treat; LVP, large volume paracentesis; MELD, model for end-stage liver disease; QTcF, QT interval corrected by the Fridericia formula; TIPS, transjugular intrahepatic portosystemic stent shunt.

with improved ascites control over a 14-day period [11]. It is postulated that satavaptan, together with spironolactone, is able to enhance ascites reduction by increasing free water excretion in patients with cirrhosis irrespective of the presence of hyponatraemia over a longer time period.

Therefore, the aim of this study was to assess the efficacy of satavaptan at three fixed doses on ascites recurrence after an LVP in cirrhotic patients with recurrent ascites being treated with spironolactone over a 12-week period.

Patients and methods

Patients

Cirrhotic patients with ascites, with or without hyponatraemia, who had at least one LVP in the previous 3 months, as well as undergoing a LVP on the day of entry, each of $\geqslant$ 4 L, were assessed for enrolment.

Exclusion criteria were serum bilirubin >135 μmol/L, international normalized ratio (INR) >3.0, serum creatinine >175 μmol/L, serum sodium >142 mmol/L, serum potassium $\geqslant$ 5.5 mmol/L, or systolic arterial pressure of <80 mmHg. Clinical exclusion criteria were significant cardiac diseases such as recent myocardial infarction ($\leqslant$1 month), or prolonged QT interval corrected by the Fridericia formula (QTcF) of $\geqslant$500 ms; complications of liver cirrhosis such as recent infection including spontaneous bacterial peritonitis, or gastrointestinal bleed ($\leqslant$10 days from randomisation), or ongoing hepatic encephalopathy of >grade 1 [12], or known hepatocellular carcinoma of >5 cm in maximal diameter for 1 lesion or <3 cm for each of $\leqslant$3 lesions. Patients who had a liver transplant, or a portosystemic shunt were not eligible, as were patients with non-cirrhotic ascites.

Methods

The study was designed and developed by the Internal Medicine team at Sanofi-Aventis, together with Drs. Wong and Gines. Dr. Wong prepared the first and subsequent drafts of the manuscript with Dr. Bernardi. The data are held and analyzed by Sanofi-Aventis, but accessible to Drs. Wong and Gines. Decisions relating to the final draft were made by Drs. Wong and Watson.

Ethics approval was obtained from all participating institutions. All patients gave written informed consent. The study was registered on a public clinical trial registry website, www.ClinicalTrials.org, number NCT 00501384.

This was a double-blind, randomised, placebo-controlled, parallel-group study assessing the efficacy of three fixed doses of satavaptan, 5, 12.5, and 25 mg versus placebo, plus low-dose spironolactone, in the prevention of ascites recurrence after a LVP of $\geqslant$4 L. On day −1, whilst inpatients, all patients underwent a complete physical examination, and a LVP of $\geqslant$4 L, plus albumin infusion at 6–8 g/L of ascitic fluid removed [4], together with complete biochemistry, a complete blood count and an electrocardiograph to exclude prolonged QTc. A 24-h urine collection was done to determine urinary volume, osmolality and electrolyte excretion. The following day (day 1), eligible patients were randomised to receive a single daily dose of either 5, 12.5 or 25 mg of satavaptan or placebo, plus 100 mg spironolactone per day for a total of 12 weeks. A central randomisation list was generated electronically at Sanofi-Aventis with each site receiving a block of equally distributed sealed treatment groups. At randomization, the lowest available treatment number at that particular site was selected for the patient, thus ensuring a random allocation of patients to each treatment group.

On days 1–3, patients were assessed clinically daily, as well as for serum electrolytes, renal function, serum and urinary osmolality, urinary volume and urinary electrolyte excretion. Patients were discharged on day 3, if possible. Outpatient visits occurred on days 7, 14, 28, 56, and 84, when the same laboratory parameters that were assessed during the first 3 days were repeated. 24-h urine collections were only done on days 28 and 84. Plasma vasopressin, supine aldosterone and supine plasma renin levels were measured on day 1 prior to study medication, and again on days 7 and 84. An electrocardiograph was repeated on days 2, 7, 28, and 84 of the study. LVP was permitted, plus albumin infusion at a dose of 6–8 g/L of ascitic fluid removed if patients had gained $\geqslant$4 kg in weight, accompanied by tense ascites. Patients were maintained on a sodium restriction of $\leqslant$88 mmol/day and were instructed to drink water as required by thirst. Throughout the study, patients were assessed for electrolyte abnormalities, renal dysfunction, dehydration and thirst.

The co-primary endpoints were time to the first paracentesis, and increase in ascites as assessed by the increase in body weight and cumulative volume of ascites removed during the 12-week study period. Secondary endpoint was frequency of paracentesis. Subgroup analysis of patients with refractory ascites was performed.

Laboratory assays

Serum and urinary electrolytes, complete blood count, INR, and liver function tests were performed using standard automated laboratory techniques. Blood samples for vasopressin, plasma renin, and aldosterone concentrations were collected on ice. Plasma was separated by refrigerated centrifugation and stored at −70 °C until assay. Serum and urinary osmolality were measured with a freezing point osmometer. Plasma renin was measured using an immuno-chemiluminometric assay (Nichols Kit & Instrument, San Clemente, CA). Plasma aldosterone (Coat-A-Count Aldosterone kit, Diagnostic Products Corporation, Los Angeles, CA), and vasopressin (Quest Diagnostics, Madison, NJ) were assayed by radioimmunoassay.

Sample size calculation and statistical analysis

Sample size calculations were based on the two co-primary endpoints. For the first primary endpoint, it was assumed that the time to first paracentesis was >12 weeks in 20% of placebo patients, versus 60% of satavaptan patients, the number required for each group would be 33 patients, or 132 patients for the four study groups. For the second primary endpoint, it was assumed that placebo patients would gain 4 kg more ascites over the 12-week period versus satavaptan patients. The number required for each group would be 35 patients, or 140 patients for the four study groups. The primary analysis was conducted on the intent-to-treat (ITT) population. Cumulative mean number of paracenteses as a function of time was estimated using the Nelson–Aalen estimator (an extension of the Kaplan–Meier estimator for recurrent events). Comparisons between treatment groups were performed using a Cox model for recurrent events with robust estimate of the variance (sandwich estimate) [13]. Change from baseline in 24-h urine volume was analysed using an analysis of covariance with treatment group as main factor and baseline value as covariate. Categorical variables were compared using the Fisher's exact test. Calculations were performed with the statistical program SAS 8.2 (Cary, NC, USA). Results are presented as mean ± SD. Median values with ranges were presented for nonparametric variables. $p < 0.05$ was considered statistically significant.

Results

Of 173 potentially suitable patients who were consented and screened between April 2004 and February 2005, 20 patients did not meet inclusion/exclusion criteria. One patient withdrew consent, and one patient did not return for randomisation. Therefore, 151 patients were entered into the study, randomised to receive placebo ($n = 36$), 5 mg ($n = 39$), 12.5 mg ($n = 36$) or 25 mg ($n = 40$) of satavaptan (Fig. 1). Patient demographics, baseline laboratory parameters are presented in Tables 1 and 2, respectively.

Control of ascites

Ascites was previously present in all patients for a mean period of >1 year (placebo: 16.7 ± 17.3 months, satavaptan 5 mg: 19.5 ± 20.2 months, 12.5 mg: 27.6 ± 30.9 months, 25 mg: 33.1 ± 36.0 months), with a previous median frequency of LVP of every 15 days (Table 1). The median time to the first LVP was increased to 23 days [95% confidence interval (CI): 16, 31 days], 26 days [95% CI, 16, 56 days] and 17 days [95% CI: 14, 28 days] with 5, 12.5, and 25 mg of satavaptan, respectively, versus 14 days with placebo [95% CI: 8, 29 days] (NS for all doses). The mean increase in ascites was 2.82 ± 0.48 L/week for placebo versus 2.12 ± 0.40, 2.14 ± 0.33, and 2.06 ± 0.40 L/week for the 5, 12.5, and 25 mg of satavaptan respectively (NS for all doses), with respective relative risks for a first repeat LVP of 0.69, 0.60, and 0.63 for the three satavaptan doses.

Over the 12-week study period, the total number of LVPs, adjusted for the duration of assessment, was significantly reduced at each dose of satavaptan: 3.11 LVPs ($p = 0.026$), 2.95 LVPs ($p = 0.018$) and 2.72 LVPs ($p = 0.017$) for 5, 12.5, and