UNIVERSITAT DE BARCELONA

Prognostic value and treatment of hyponatremia in patients with advanced cirrhosis and acute on chronic liver failure

Andrés Cárdenas Vásquez

Prognostic value and treatment of hyponatremia in patients with advanced cirrhosis and acute on chronic liver failure

Doctoral Thesis 2015

Andrés Cárdenas Vásquez

UNIVERSIDAD DE BARCELONA

Facultad de Medicina

DIRECTOR: **Dr. Pere Gines i Gibert**

Cap de Servei d' Hepatologia
Institut de Malalties Digestives i Metaboliques
Hospital Clínic Barcelona. IDIBAPS. CIBERehd
Universitat de Barcelona

AUTHOR: **Andrés Cárdenas Vásquez**

Gastroenterology Department
Institut de Malalties Digestives i Metaboliques
Hospital Clínic Barcelona.
Universitat de Barcelona

Acknowledgements

I want to deeply thank my wife and son for putting up with all my research activities throughout the years.

I want to specially thank Dr Pere Gines for his support and mentorship all these years. He is certainly has been one of the most positive influences in my professional career; I can't thank him enough.

I want to thank Dr Vicente Arroyo for his mentorship and support, he is one of the main reasons I came to Barcelona.

I wish to thank all my colleagues in the Liver, GI, and Endoscopy and Units as they have played a key part of my professional activities since I arrived in Barcelona.

I also want to thank all the nurses in the Endoscopy unit and the wards for helping me take care of patients all these years.

I want to thank Marco Pavesi for his patience and expert statistical support

I want to thank the secretarial staff of the Institute for all their help and support.

Finally I would like to thank all the patients that have participated in the studies presented in this thesis.

INDEX:

Abbreviations:

HRS: hepatorenal syndrome

RAAS: renin-angiotensin-aldosterone system

SNS: sympathetic nervous system

AVP: arginine vasopressin

AQP: aquaporins

MELD: Model for End-Stage liver disease

HRQL :health related quality of life

ACLF :acute on chronic liver failure

CLIF SOFA : Chronic Liver Failure Sequential Organ Failure Assessment

CANONIC: CLIF Acute-oN-ChrONic LIver Failure in Cirrhosis Core Study

SIADH: syndrome of inappropriate antidiuretic hormone secretion

1. INTRODUCTION

The mechanisms responsible for fluid retention in patients with liver disease have interested physicians throughout the history of medicine. The Egyptians and Greeks believed that there was a relationship between liver disease and ascites. In 300 BC Erasitratus of Cappadoccia, described ascites as a consequence of "hardness of the liver" or liver disease (1,2). The term ascites derives from the Greek root "askos", meaning bag. Several centuries later physicians discovered the relationship between advanced liver disease and the development of ascites. Numerous studies addressing this issue have shown that alterations in systemic and splanchnic circulation as well as functional renal abnormalities are the culprit of fluid accumulation in patients with cirrhosis.

In the natural history of cirrhosis, patients may develop significant complications of renal function manifested initially by increased sodium retention followed by impaired solute-free water excretion, and finally with renal vasoconstriction (3). These alterations are responsible for fluid accumulation in the form of ascites, hyponatremia and hepatorenal syndrome (HRS) respectively. Ascites is the most common complication of cirrhosis resulting in poor quality of life, increased risk for infections, renal failure and mortality. The development of ascites in cirrhosis is a poor prognostic feature because it has been estimated that approximately half of these patients will die in approximately 4 to 5 years without liver transplantation (4,5). Therefore the presence of ascites, hyponatremia or HRS in a cirrhotic patient is considered an indication for liver transplantation (6).

Renal abnormalities in cirrhosis occur in the setting of a hyperdynamic state characterized by an increased cardiac output, a reduction in total vascular resistance and an activation of neurohormonal vasoactive systems (7). This circulatory dysfunction, a consequence of intense arterial vasodilation in the splanchnic circulation is considered a primary feature in the pathogenesis of ascites. The main factor responsible for local splanchnic vasodilation is mainly an overproduction of extrahepatic endothelial nitric oxide synthase (eNOS) derived nitric oxide (NO), although other factors such as endocannabinoids, carbon monoxide, adrenomedullin, and prostacyclin among others have been implicated in the pathophysiology of this vasodilation (8). Splanchnic vasodilation by decreasing effective arterial blood volume will then cause a homeostatic activation of vasoconstrictor and antinatriuretic factors triggered to compensate for a relative arterial underfilling in order to increase blood pressure (9). The net effect is avid retention of sodium and solute-free water as well as renal

vasoconstriction in advanced stages. These events described above are the basis for the Arterial Vasodilation Theory (9) which is summarized in **Figure 1.** This is the most accepted theory that explains the events that lead to sodium and water retention in cirrhosis and that finally culminate with renal vasoconstriction.

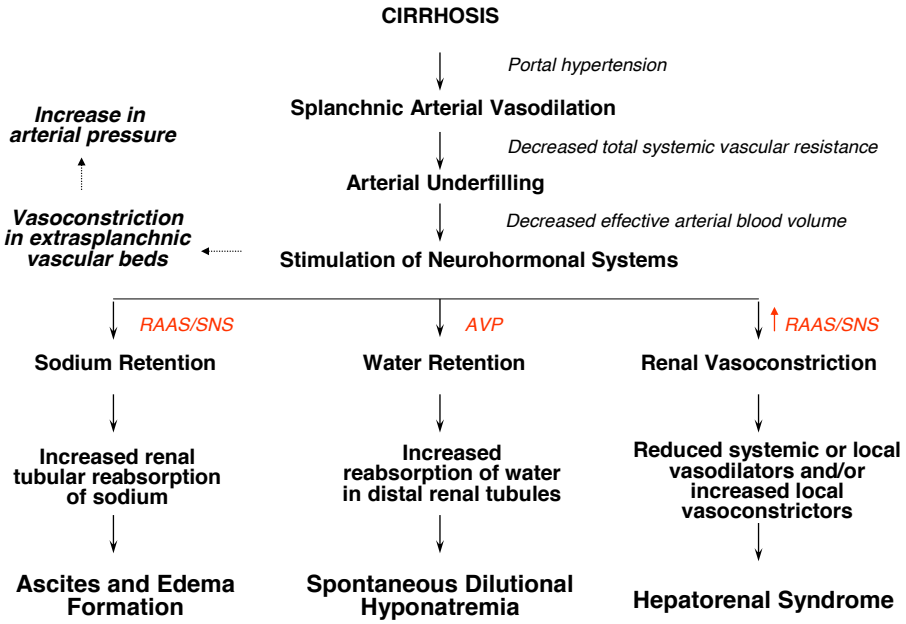


Figure 1. The pathogenesis of ascites formation and renal dysfunction according to the Arterial Vasodilation theory. The neurohumoral effects of the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), and arginine vasopressin (AVP) on systemic circulation and renal function in cirrhosis with ascites are responsible for sodium and water retention as well as hepatorenal syndrome. The levels of these vasoconstrictors are highest in patients with hepatorenal syndrome

1.1. Functional renal abnormalities

Most derangements of renal function that occur in patients with cirrhosis are pathophysiologically related to the presence of an expanded extracellular fluid volume which leads to the development of ascites and/or edema. These renal abnormalities occur in the setting of a hyperdynamic state along with activation of vasoactive systems. This circulatory dysfunction, a consequence of intense arterial vasodilation in the splanchnic circulation is

considered a primary feature in the pathogenesis of sodium and solute-free water retention in cirrhosis. Sodium retention is the main factor responsible for ascites and edema formation, whereas impairment in solute-free water excretion is responsible for the development of hypervolemic hyponatremia. Sodium retention with ascites accumulation appears first, later followed by the development of solute-free water retention and finally renal vasoconstriction that with disease progression leads to HRS (10) – **Figure 2**.

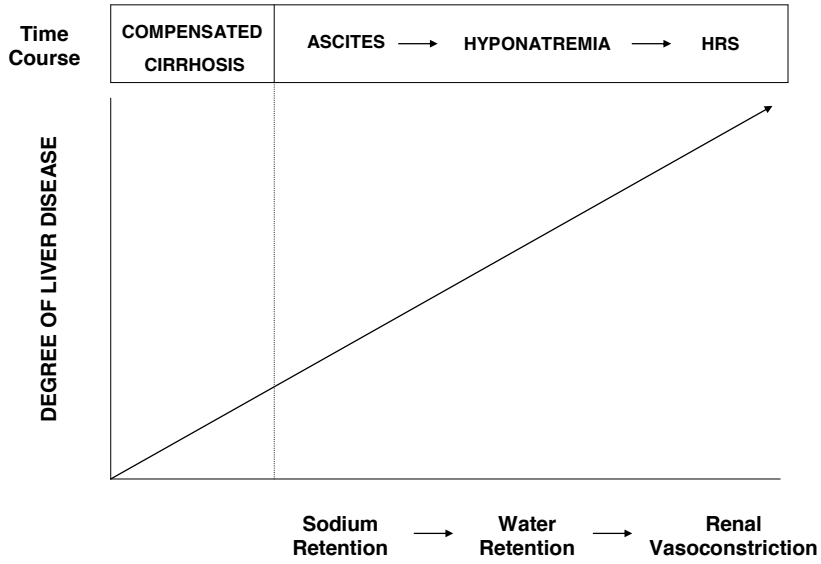


Figure 2. Temporal relationship of sodium and solute-free water retention and renal vasoconstriction and the relationship with ascites, hyponatremia and hepatorenal syndrome(HRS).

Patients without the development of any of the major complications of cirrhosis such as ascites, variceal hemorrhage, or hepatic encephalopathy have very subtle abnormalities in renal sodium metabolism. For example they may be unable to excrete a sodium overload, as occurs in hospitalized patients with cirrhosis that receive intravenous saline infusions. However, with time cirrhotic patients develop an inability to excrete their regular sodium intake and develop sodium retention. This derangement precedes the onset of ascites indicating that it is a cause and not a consequence of fluid retention (11). In advanced cirrhosis sodium retention further leads to the expansion of extracellular fluid volume and an increased amount of fluid in the interstitial tissue. The pathogenesis is due to an abnormally increased reabsorption of sodium in the renal tubules (proximal and distal) because it occurs in the setting of a normal filtered sodium load (12). The three major hormones acting on the renal

tubules that contribute to sodium retention are aldosterone, angiotensin and norepinephrine. Solute-free water retention in advanced cirrhosis develops after the onset of sodium retention and is mainly due to elevated levels of arginine vasopressin (AVP) (3,13). Hypervolemic hyponatremia occurs despite avid sodium retention because water is retained in excess of sodium. Renal vasoconstriction is the renal functional abnormality that develops latest in patients with cirrhosis and ascites. The clinical consequence is the development of HRS, which occurs in the late stages of cirrhosis.

1.2 Definition of hyponatremia in cirrhosis

Hyponatremia in the general population is defined as a serum sodium level below 135 mEq/L (14,15). However, hyponatremia in cirrhosis is defined as a serum sodium concentration of less than 130mEq/L in the presence of ascites or edema (16-18). This definition has been agreed upon by expert and consensus guidelines (18). Although a significant proportion of patients with cirrhosis have a serum sodium concentration above 130 mEq/L and below 135 mEq/L; these patients may display pathogenic and clinical features similar, yet less pronounced, to those of patients with serum sodium below 130 mEq/l. That said, the threshold for treating hyponatremia in cirrhosis has been considered a level below 130 mEq/L, thus this is the most accepted definition in patients with cirrhosis (16-18)

1.3 Types of hyponatremia in cirrhosis

Patients with cirrhosis may develop either hypervolemic or hypovolemic hyponatremia. Hypervolemic or dilutional hyponatremia is the most common type that occurs in patients with cirrhosis and it occurs in the setting of an expanded extracellular fluid and plasma volume. Hypervolemic hyponatremia in cirrhosis is due to a marked impairment in the renal capacity to eliminate solute-free water leading to disproportionate water retention with respect to sodium retention (19). It may occur spontaneously or as a consequence of excessive hypotonic fluids (for example, by giving an undue amount of iv hypotonic fluids – 5% dextrose – during a hospitalization) or other complications of cirrhosis such as in the setting of some bacterial infections (19,20). By contrast, hypovolemic hyponatremia is less common and is due to significant losses of extracellular fluid, particularly from the kidney due to overdiuresis from diuretic treatment or from gastrointestinal tract. Hypovolemic

hyponatremia is characterized by a reduction of plasma volume, lack of ascites and/or edema, signs and dehydration and prerenal renal failure. Most patients with hypovolemic hyponatremia show an improvement of serum sodium levels after the administration of normal saline.

1.4 Pathogenesis of hyponatremia

In healthy subjects, total body water is maintained within tight limits despite variations in daily fluid intake. Any increase in water intake is followed by an increase in renal solute-free water excretion, preventing the development of hypoosmolality. In contrast, a decrease water intake is associated with diminished solute-free water excretion in order to prevent hyperosmolality and dehydration. These variations in water excretion depend on the osmoreceptors located in the hypothalamus to detect changes in plasma osmolality and on effector mechanisms to induce the appropriate modifications in the kidneys. Patients with cirrhosis and ascites frequently have impairment in the renal capacity to eliminate solute-free water. In some patients, the impairment in solute-free water excretion is moderate. These patients are able to eliminate water normally and maintain a normal serum sodium concentration as long as their water intake is kept within normal limits, but they may develop hyponatremia if water intake is increased. In other patients, the severity of the disorder is so intense that they retain most of the water ingested, and this causes hyponatremia and hypoosmolality.

The pathogenesis of increased solute-free water retention in cirrhosis is intricate and involves several factors, including high levels of AVP, reduced synthesis of renal prostaglandins, and reduced delivery of filtrate to the ascending limb of the loop of Henle (16,17). Among these, increased AVP is the most important factor in the pathogenesis of water retention in patients with cirrhosis and ascites (21). In cirrhosis, splanchnic vasodilation leads to arterial underfilling which unloads high-pressure baroreceptors that stimulate a non-osmotic hypersecretion of AVP leading to solute-free water retention and hyponatremia (**Figure 3**).

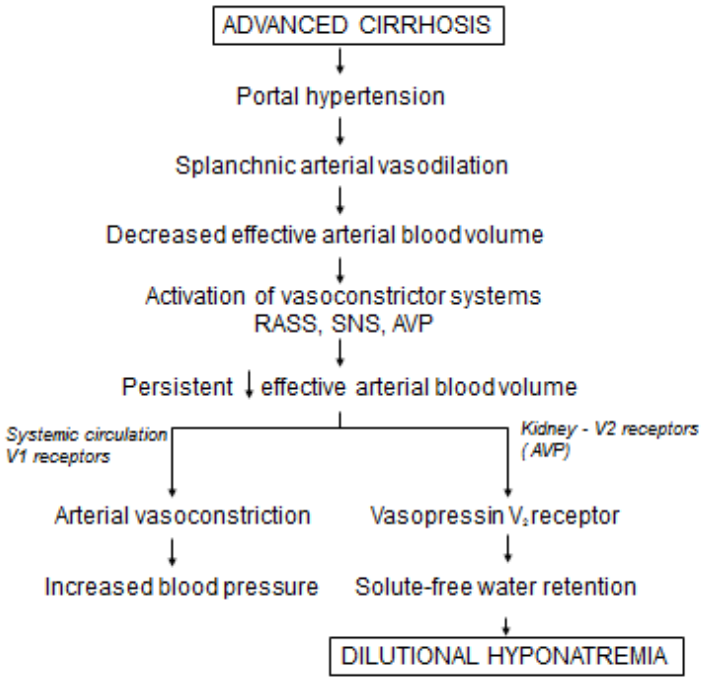


Figure 3. *Proposed pathogenesis of hypervolemic hyponatremia in cirrhosis. There is activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) and a nonosmotic hypersecretion of arginine vasopressin (AVP) due to decreased effective arterial blood volume that activates baroreceptors and stimulates the hypothalamic release of AVP causing renal solute-free water retention through the action of V2 receptors and arterial vasoconstriction through the action of V1 receptors*

The physiological actions of AVP are exerted through three types of receptors present in target cells throughout the body (22). These receptors are G protein-coupled receptors known as V1a, V1b and V2 receptors. V1a and V1b are associated with the phosphoinositol signaling pathway with intracellular calcium as second messenger. V1a is responsible for vascular smooth muscle cell contraction, platelet aggregation and hepatic glycogenolysis and V1b is expressed in the anterior pituitary where it intervenes in adrenocorticotropin release (22). The V2 receptors are located on the basolateral (capillary) membrane of the principal cells of the kidney collecting ducts and are responsible for the AVP-induced solute-free water reabsorption (21,22). The effect of AVP in the kidney collecting duct occurs by means of specific water channels called aquaporins (AQP). The most important one in solute-free water retention is AQP2. This water channel has been characterized in human and rat kidneys and is expressed almost exclusively in the principal cells of the collecting ducts (23,24). The binding

of AVP to the V2 receptor stimulates adenyl cyclase via the stimulatory G protein and promotes the formation of cyclic AMP (cAMP). This cAMP binds to a regulatory subunit of protein kinase A, which in turn phosphorylates AQP2, which is then translocated from vesicular bodies present in the cytosol to the luminal (apical) plasma membrane of the collecting duct cells, and acts as a water channel thereby increasing water permeability (21,22). The water entering the cell by the luminal plasma membrane leaves the cell through the basolateral membrane and enters the capillaries in contact with the tubular cells as shown in **Figure 4**.

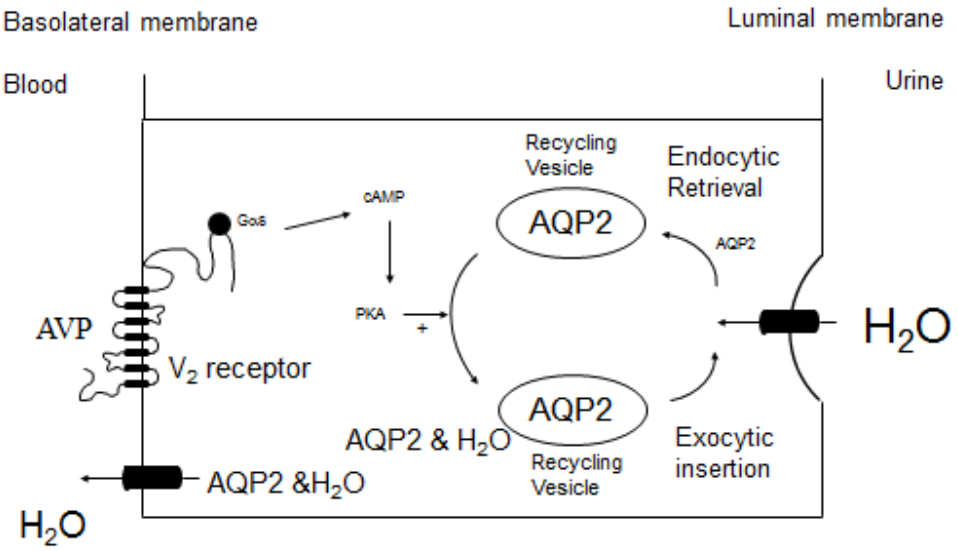
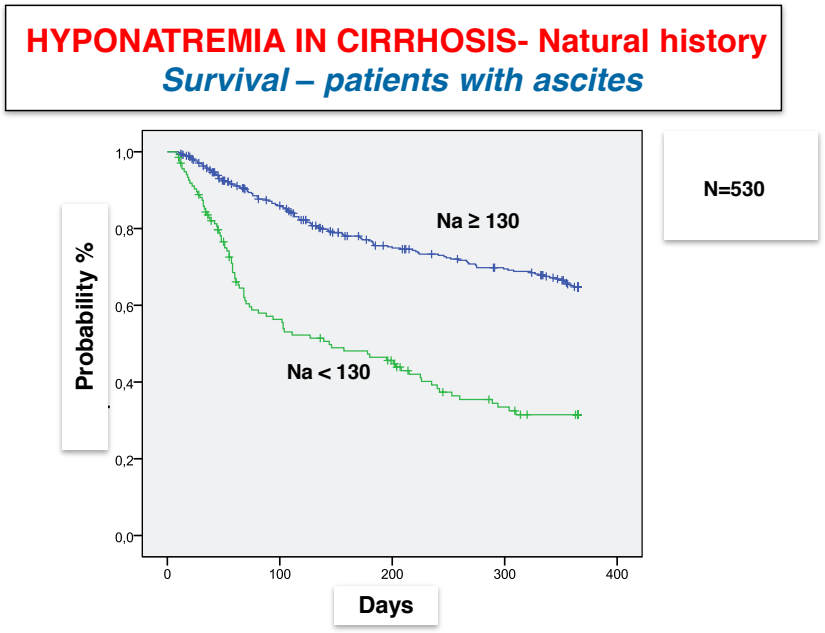


Figure 4. Schematic drawing of the collecting duct principal cell and the intracellular action of AVP. The hormone binds to the V2 receptor in the basolateral membrane and activates adeylyl cyclase with generation of cAMP. Protein kinase (PKA) is the target of cAMP, which then phosphorylates AQP2. This water channel is translocated in cytoplasmatic vesicles to the luminal membrane, thereby increasing water permeability.

Data from patients with cirrhosis and hypervolemic hyponatremia in whom V2 receptor antagonists of AVP (vaptans) were administered indicate that hypersecretion of AVP plays a major role in the development of hyponatremia because these drugs increase in serum sodium concentration in a large proportion of patients (25,26).

1.5 Prognosis of hyponatremia

Patients with cirrhosis and hyponatremia have a 30-40% probability of survival at 1 year and 23 % at 5 years (4,27,28) (**Figure 5**). It is estimated that more than 20% of patients with advanced cirrhosis have serum sodium levels < 130 mEq/L, however in patients with refractory ascites or HRS, this proportion may increase to more than 50% (29,30). In the majority of patients, hyponatremia occurs in close association with an impairment of renal function and correlates with poor prognosis (31,32). A number of studies also indicate that hyponatremia is an important marker of prognosis in patients with cirrhosis awaiting liver transplantation and may be associated with an increased morbidity, particularly neurological complications, and reduced survival after transplantation (33-36).



Cardenas A, Gines P, Schiff 's Diseases of the Liver 2007

Figure 5. Survival of patients with cirrhosis and ascites with and without hyponatremia.

Hyponatremia in cirrhosis has been clearly described as an independent risk factor for mortality (33,37,38) and is common in patients with end-stage liver disease. In a study of 997

cirrhotic patients (29) the prevalence of serum sodium ≤ 130mmol/L was 22% and this patient subgroup had a significantly higher incidence of hepatic encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis. There was also a higher rate of refractory ascites and requirement for frequent therapeutic paracentesis proportional to the level of serum sodium <135mmol/L. Serum sodium and the Model for End stage Liver Disease (MELD) score have both been shown to predict mortality in patients with advanced cirrhosis on the liver transplant waiting list (34,39). Combining serum sodium with MELD (MELD-Na) has been shown to more accurately predict mortality on the waiting list compared to MELD score alone (39-41).

1.6 Clinical features of hyponatremia

There is limited data on the clinical consequences of hypervolemic hyponatremia in cirrhosis because hyponatremia occurs in the setting of advanced liver failure and patients may present with a range of nonspecific symptoms attributed to their underlying cirrhosis. However there is a clear relationship between hyponatremia and neurological symptoms and other complications of cirrhosis.

1.6a Neurological symptoms

In patients without liver disease, hyponatremia is primarily associated with a wide range of neurological manifestations related to brain edema such as headache, confusion, focal neurological deficits, seizures, and, in some cases, death due to cerebral herniation (14). The severity of neurological symptoms in patients with hyponatremia without liver disease correlates with the levels of osmolality and sodium in the extracellular fluid. Nevertheless, rather than the absolute reduction in serum sodium levels, the most important factor in determining the severity of neurological symptoms is the rate of fall in serum sodium levels (14,15). Patients with acute hyponatremia have a higher incidence of neurological symptoms than those with chronic hyponatremia. There are no studies that have specifically evaluated neurological symptoms in patients with cirrhosis and hyponatremia. However, in most patients neurological manifestations such as headache, focal deficits, seizures, and cerebral herniation are very uncommon. It is likely that the relatively low incidence of neurological manifestations in patients with cirrhosis and hypervolemic hyponatremia is related to the fact

that most of these patients have chronic hyponatremia which gives sufficient time for brain adaptation to hypo-osmolality. In most patients with cirrhosis, hyponatremia is asymptomatic, but some data indicate that hyponatremia is associated with a higher risk of hepatic encephalopathy (42-44). Although not precisely known, the mechanism by which hyponatremia is associated with hepatic encephalopathy is likely due to changes in serum osmolality that lead to astrocyte swelling and then cellular release of solutes as a response to prevent cell swelling and cerebral edema (**Figure 6**). These changes are relevant because the underlying pathogenesis of hepatic encephalopathy in cirrhosis is felt to be based on the fact that ammonia and other toxins induce a low-grade cerebral edema due to astrocyte swelling secondary to increased intracellular levels of glutamine that alter astrocyte function (45). Consequences of astrocyte swelling include alterations in gene expression and oxidative stress that alter glioneuronal communication and disturb neurological function, leading to encephalopathy (46). Thus the presence of hyponatremia in combination with hyperammonemia, by favoring astrocyte swelling, may increase the risk of hepatic encephalopathy.

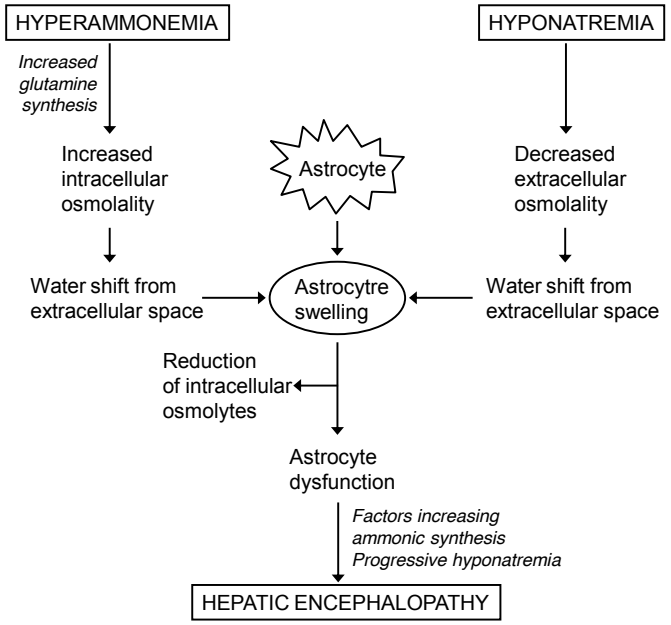


Figure 6. *Proposed interaction between hyperammonemia and hyponatremia on brain astrocytes and possible pathogenic relationship with hepatic encephalopathy*

1.6 b Complications of cirrhosis

Aside from hepatic encephalopathy, hyponatremia is also associated with other complications of cirrhosis, yet information is limited. Hyponatremia is a frequent finding in patients with cirrhosis and bacterial infections and a marker of poor outcomes of patients hospitalized with infections. Spontaneous bacterial peritonitis (SBP) is often associated with significant morbidity including renal failure and has a high mortality rate in published series. Patients with hyponatremia at diagnosis of SBP are at much higher risk for development of hepatorenal syndrome and death (47,48). Also, in the majority of patients, hyponatremia occurs in close association with renal failure and correlates with poor prognosis. For instance, the incidence of hyponatremia and renal failure in cirrhotic patients admitted for skin and soft tissue infection is higher than in matched cirrhotic controls without infection and is associated with higher 3 month mortality compared to patients without the development of hyponatremia and renal failure (45% vs. 19%) (20). Moreover, it is important to note that patients with ascites and hyponatremia constitute a population with a very high risk of developing HRS (31,48). On the other hand, low serum sodium levels are a common finding in patients with HRS.

Information on the impact of hyponatremia on health-related quality of life in patients with liver disease is limited. In patients with cirrhosis, hyponatremia impairs quality of life because patients require a restriction of daily fluid intake to prevent further reductions in serum sodium concentration, and this is usually poorly tolerated. Moreover, in a recent study in a large population of patients with cirrhosis and ascites, hyponatremia was an independent predictive factor of the impaired health-related quality of life (49). Low serum sodium has been shown to have a negative impact on the quality of life in patients with cirrhosis and ascites. A recent cross sectional study of 523 patients with cirrhosis complicated by ascites demonstrated that health related quality of life (HRQL) was significantly decreased in patients with hyponatremia and serum sodium less than 130 mEg/L (49). This effect was independent of disease severity marked by liver failure or increased MELD score. Interestingly, there was a significant impairment in the HRQL even in patients with mild hyponatremia with serum sodium falling between 130mEq/L and 135mEq/L. In addition, recent data point to hyponatremia as a strong predictor of poor HRQL independent of overt cognitive dysfunction, and this may be improved following withdrawal of diuretics in the sub-group of patients

whose serum sodium responds to this intervention (50). Finally in patients with cirrhosis and hyponatremia correction of hyponatremia by pharmacological means is associated improvement in cognitive function, health related quality of life and companion burden (51).

Pre-transplantation serum sodium in patients with cirrhosis has been shown to predict overall poor outcomes and increased mortality following orthotopic liver transplant. In one series there was a significant increase in the relative number of cases of central pontinemyelinolysis following transplant in those patients with serum sodium < 125mmol/L compared to those with normal serum sodium (4.6% vs. 0.1%, p<0.01) with a low absolute number of cases among all patients receiving transplant (0.5%) (52).One series of 241 patients listed for transplant evaluated the effect of hyponatremia (Na <130mEq/L) on early post-transplant outcomes including 3-month survival and complications including infection, neurological disease, and renal failure (35). Post-transplant survival at 3 months was significantly reduced in those patients with hyponatremia prior to transplant (84% vs. 95%, P<0.05) with equivalent survival following this period. The probability of renal failure, neurologic disease, and infectious complications were also increased with OR 3.4, 4.6 and 2.7, respectively. A similar result was found in a large cohort of 5,152 transplant recipients from the United Kingdom and Ireland (36). In this series, patients undergoing transplant with hyponatremia and a serum sodium < 130mEq/L were found to have a higher risk adjusted mortality at 90 days post-transplant compared to controls with normal sodium.

1.7 Management of hyponatremia

The first step in the management of hyponatremia in cirrhosis is to identify whether hyponatremia is hypovolemic or hypervolemic, because the management is completely different according to the type of hyponatremia. The management of hypovolemic hyponatremia consists on the identification and treatment of the cause of sodium loss such as stopping diuretic therapy together with the administration of sodium (either regular saline i.v. or diet with normal sodium content). A key aspect in the management of hypervolemic hyponatremia is to increase renal solute-free water excretion with the aim of reducing the increased total body water. The advantages of treating hypervolemic hyponatremia in

cirrhosis include: avoidance of long term fluid restriction, ameliorating the risk of hepatic encephalopathy and also potentially reducing the risk of neurological complications after transplantation. The available therapeutic methods for the management of hypervolemic hyponatremia are summarized below.

Fluid and water restriction

Fluid restriction (1.5 lt/day) is still considered the first step in the management of hypervolemic hyponatremia (18,19). There are no studies specifically assessing the effectiveness of fluid restriction in this setting but it is likely necessary to prevent a progressive decrease in serum sodium levels. Fluid restriction rarely increases serum sodium concentration in a significant manner, largely because the volume restriction required to effect significant changes - generally 500 ml - is less than that tolerated by patients (53).

Sodium chloride

The use of intravenous hypertonic sodium chloride is neither advisable nor previously investigated in randomized studies of patients with cirrhosis. Hypertonic sodium chloride has a very partial and short-lived effect in improving serum sodium concentration in cirrhosis perhaps because it has no effect on renal solute-free water excretion. Moreover, it has a major drawback; that is increasing ascites and edema due to the severe sodium retention present in these patients because of the large amount of sodium given

Albumin

Two short-term studies, one in 1990 and the other only published in abstract-form, including a low number of patients suggest that the administration of albumin could improve serum sodium concentration in patients with hypervolemic hyponatremia (54,55). By improving circulatory function, albumin likely suppresses the sodium and water-retaining systems, including non-osmotic AVP release. Unfortunately, the effects of albumin infusion were studied over only 1 week. As the half-life of infused albumin is relatively short lived (15-20 days), the changes it can bring are fundamentally temporary. It is also a costly therapy. Accordingly, further studies should focus on the subset of high risk patients that would benefit

from a short-term therapy, namely those with profound hyponatremia awaiting liver transplantation.

AVP antagonists - the vaptans

The vaptans are specific drugs that are active orally and cause a selective blockade of the V2-receptors of AVP in the principal cells of the collecting ducts. In healthy subjects, the administration of vaptans induces a marked and dose-dependent increase in urine volume with low urine osmolality due to a marked increase in solute-free water excretion, but without an increase in urinary sodium excretion (56). These medications act as direct antagonists of the V2 receptor in the collecting tubule of the nephron, and significantly increase free water clearance. Tolvaptan is an orally administered V2R antagonist that is approved for use in the United States and Europe. Lixivaptan and Satavaptan have also been studied in cirrhosis and hyponatremia but are not approved in the United States or Europe. Several randomized, double-blind, comparative studies indicate that treatment with vaptans for a short period of time (up to 1 month), including tolvaptan, lixivaptan, and satavaptan, improves serum sodium concentration in patients with hypervolemic hyponatremia due to heart failure, syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cirrhosis (57,58). A small study suggests that intravenous conivaptan, a vaptan that is not only an antagonist of the V2 receptors but also of the V1 receptors of AVP, is also effective in patients with cirrhosis and hyponatremia (59).

The efficacy of tolvaptan in raising serum sodium was studied in two randomized, placebo controlled, double blind phase 3 trials (Study of Ascending Levels of Tolvaptan in Hyponatremia 1 and 2 [SALT-1 and SALT-2])(25). All patients had hypervolemic hyponatremia with serum sodium ≤ 135mEq/L with 50% of patients classified as marked hyponatremia with serum sodium < 130mEq/L. All patients were hospitalized and were randomized to tolvaptan 15mg daily or placebo with up-titration of dosing to a maximum of 60mg/d in those who failed to respond to lower doses. Serum sodium improved and reached normal levels in significantly more patients in the tolvaptan group compared to placebo ($p<0.001$). Satavaptan (26) and lixivaptan (60,61) have been evaluated in several trials of hyponatremia including cirrhotic patients that showed an improvement in hyponatremia. Unfortunately, the use of satavaptan was associated with an increased mortality in one of the

studies but not in the other two and the drug was withdrawn from development. The reason for this increased mortality could not be elucidated.

Randomized, double-blind, comparative studies indicate that treatment with vaptans in patients with cirrhosis for a short period of time improves serum sodium concentration in patients with cirrhosis and hypervolemic hyponatremia (26,60,61). The increase in serum sodium concentration usually occurs within the first 7 days of treatment (**Table 2**). Moreover, in approximately one third of additional patients serum sodium increases more than 5 mEq/L but does not reach values > 130 mEq/L.

Table 2. Short-term clinical studies using V2 receptor antagonists in patients with cirrhosis and hyponatremia.

Author (year)	Compound	Dose	Phase	Patients	Efficacy/Side effects
Wong (2003)	Lixivaptan+	50-500 mg/day po	II	44# treated for 7 days	Increased urine output, CH_2O, S osm, SNa. Dehydration with doses of 500mg. Drop-out rate - 27%.
Gerbes (2003)	Lixivaptan+	100-200 mg/day po	II	60 treated for 7 days	Increased SNa, decreased U osm and body weight. Thirst appeared in patients at the 200 mg dose.
Ginès (2008)	Satavaptan+	5mg, 12.5mg and 25mg daily	II	110 treated for 14 days	Concomitant spironolactone 100mg/day. SNa increased to ≥135mEq/L or > 5 mEq/L in 50-80% of cases.

U osm: urinary osmolality, S osm: serum osmolality, CH_2O: solute-free water clearance, SNa: Serum sodium, U vol: urine volume, AUC: area under the curve
+randomized, double-blind, placebo-controlled trial.
included 5 patients with cardiac disease and 5 with SIADH

It should be mentioned that treatment with vaptans has been assessed for the management of ascites in cirrhosis. Specifically, satavaptan was evaluated for the treatment of ascites in association with diuretics with the rationale that by increasing diuresis the vaptan would help manage ascites and prevent its recurrence. Although results of phase-2 studies were promising (62), phase-3 long-term treatment studies in three different populations of patients with cirrhosis and ascites demonstrated a lack of efficacy in both, ascites management and prevention of its recurrence (63). A small study in 18 patients with cirrhosis and ascites without hyponatremia showed that the administration of tolvaptan dose-dependently decreased body weight and improved ascites and edema (64). Finally in a randomized study 164 patients received either tolvaptan or placebo as add-on therapy to diuretics with the primary end-point of weight change at 7 days. There was a significant reduction in weight in the tolvaptan group compared to placebo (65).

The most frequent side-effect reported in studies evaluating the vaptans in patients with hyponatremia is thirst, which is related to the pharmacodynamic actions of these drugs. Nonetheless hypernatremia (serum sodium > 145 mmol/l) and dehydration occur in only 2-4% of patients with cirrhosis treated with vaptans (25,26). An important concern is to avoid a rapid increase in serum sodium that could lead to neurological complications due to osmotic demyelination syndrome. However, osmotic demyelination syndrome has not been reported in any study. Since, vaptans are metabolized by CYP3A enzymes in the liver; therefore drugs or substances that are strong inhibitors of CYP3A such as ketoconazole, grapefruit juice, and clarythromycin among others, increase the exposure to vaptans and may be associated with larger increases in serum sodium concentration. By contrast, drugs that are inducers of the CYP3A system, such as rifampin, barbiturates and phenytoin, may decrease the effectiveness of vaptans.

Vaptans seem to be effective in the short-term treatment of hypervolemic hyponatremia, however information is very limited in patients with cirrhosis. Tolvaptan is approved for the treatment of hypervolemic hyponatremia associated with SIADH, cardiac failure or cirrhosis by the Food and Drug Administration in the United States, for SIADH by the European Medicines Agency in Europe, and for diuretic-resistant volume overload in heart failure by the

Ministry of Health in Japan. Data from pivotal studies of tolvaptan that enrolled patients with hypervolemic hyponatremia due several causes indicate that tolvaptan effectively improves serum sodium levels in these patients (25,66,67). Tolvaptan is recommended for the management of severe (<125 mmol/l) hypervolemic hyponatremia. Treatment of tolvaptan is started with 15 mg/day and titrated progressively to 30 and 60 mg/day, if needed, according to the desired changes in serum sodium concentration. The safety and efficacy of tolvaptan has only been reported for a short-treatment period (30 days) and the results indicate that mean serum sodium levels increased during the first 7 days and were maintained above 130 mEq/L during 30 days (25). In these studies, no evaluation was performed according to the disease responsible for hyponatremia. Thus, there is lack of data on the specific effects of tolvaptan in patients with cirrhosis and hyponatremia.

1.8 Acute on chronic liver failure

1.8a Definition

Patients with cirrhosis that develop acute complications such as ascites, hepatic encephalopathy, hyponatremia, gastrointestinal bleeding, and/or bacterial infections can be classified into those with mere decompensated cirrhosis and those in whom an acute event ifs followed with progressive liver and/or extrahepatic organ failure(s). These latter patients have a poor prognosis and have been defined as having acute on chronic liver failure (ACLF) (68). ACLF defines a subgroup of cirrhotic patients who develop organ failure(s) following hospital admission with or without an identifiable precipitating event. The current definition established by the World Gastroenterology Organization considers ACLF a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of INR [International Normalized Ratio]) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset (69). The definition is mainly based on a large prospective, multicenter, observational study carried out by the EASL – CLIF consortium in 8 European centers (70). In the study, the authors were able to outline and differentiate patients with ACLF from those without ACLF (i.e. patients with a mere decompensation) according to pre-specified criteria that were prospectively validated. The study enrolled 1343 patients with cirrhosis from several European countries between February and September 2011. Acute decompensation was defined by development of gastrointestinal hemorrhage, bacterial infections, large ascites or any combination of these events. The investigators then used a modified SOFA score (CLIF-SOFA score) to define organ failure(s). This scale was designed prior to the onset of the study and it assessed the function of 6 systems (liver, kidneys, brain, coagulation, circulation and lungs) (**Figure 7**). ACLF was then diagnosed based on a predefined 28-day mortality rate of 15% or greater. Renal failure was associated with higher mortality compared to any other single organ failure. Also the importance of extrahepatic organ failure for diagnosis of ALCF was demonstrated by a lower mortality rate (4%), for example, in patients with significantly elevated serum bilirubin without any extrahepatic damage. In the study, the overall prevalence of ACLF was 30.9% with a 90 day mortality rate of 49% (70). Among the many variables analyzed as risk factors in relation to the abovementioned organ systems, ascites, and a high leukocyte count were found to be predictive for the development of ACLF and ACLF associated mortality, nonetheless other factors such as hyponatremia were not found to be

predictive. ACLF episodes are responsible for a large proportion of the health care costs attributable to acute decompensation of cirrhosis. Consequently, the development of ACLF is an important outcome and its prevention is a key component of cirrhosis management.

Organ/system (Points)	**0**	**1**	**2**	**3**	**4**
Liver (Bilirubin, mg/dL)	<1.2	≥1.2 - ≤1.9	≥2 - ≤5.9	≥6 - <12	≥12
Kidney (Creatinine, mg/ dL)	<1.2	≥1.2 - ≤ 1.9	≥2 - <3.5	≥3.5 - <5	≥5 or use of renal-replacement therapy
Cerebral (HE grade)	No HE	1	2	3	4
Coagulation (INR)	<1.1	≥1.1 – <1.25	≥1.25 - <1.5	≥1.5 – <2.5	≥2.5 or Platelets≤20x10^9/L
Circulation (MAP mm Hg)	≥70	<70	Dopamine ≤5 or Dobutamine or Terlipressin	Dopamine >5 or E ≤ 0.1 or NE ≤ 0.1	Dopamine >15 or E > 0.1 or NE > 0.1
Lungs PaO2/FiO2: or SpO2/FiO2	>400 >512	>300 - ≤400 >357 - ≤512	>200 - ≤300 >214 - ≤357	>100 - ≤200 >89- ≤214	≤100 ≤89

Figure 7- *CLIF SOFA score that defines organ failure in ACLF*

1.8b Precipitating events

One of the most important features of ACLF is the association with precipitating events that lead to an acute hepatic decompensation (Table 1). However a precipitating factor cannot be identified in 45% of patients with ACLF admitted to the hospital. Most events are either ischemic or infectious in nature, and the inflammatory response seems to play an important role in the outcomes of ACLF. The CANONIC Study demonstrated that elevated serum C-reactive protein (CRP) and/or an increased leukocyte count are associated with worse outcomes. In fact, the severity of ACLF-grade correlated directly with the degree of inflammation thus indicating that ACLF is associated with marked systemic inflammation. However other factors such low serum sodium levels were not specifically assessed as potential precipitating events that influenced outcome (70,71).

Table 1. Precipitating events in patients with ACLF

1. Viral Hepatitis (Acute hepatitis A, E, hepatitis D on chronic hepatitis B)
2. Acute Alcoholic Hepatitis
3. Bacterial Infections
4. Gastrointestinal Bleeding
5. Major Surgery
6. Drug-Induced Liver Injury
7. Insertion of Transjugular Intrahepatic Portosystemic Shunt
8. Large volume paracentesis without intravenous albumin administration
9. Hypovolemia / Hypotension
10. Portal Vein Thrombosis
11. Idiopathic

1.8c Classification

Patients with cirrhosis can be classified into four groups, based on the association of organ failure(s) with short-term (28 day) mortality: no ACLF, ACLF grade 1, grade 2 and grade 3. The diagnosis and prognosis directly relies on the number of organ failures. In fact, patients with no organ failure (no ACLF) have a very low 28 and 90-day mortality rate (<5-10%), those with 1 organ failure have a 20-40% mortality rate , while patients with 2 organ failures (ACLF grade 2) or those with 3 organ failures or more (ACLF grade 3) have a high mortality rate (32 -55% and 78-80%, respectively). **Figure 8**

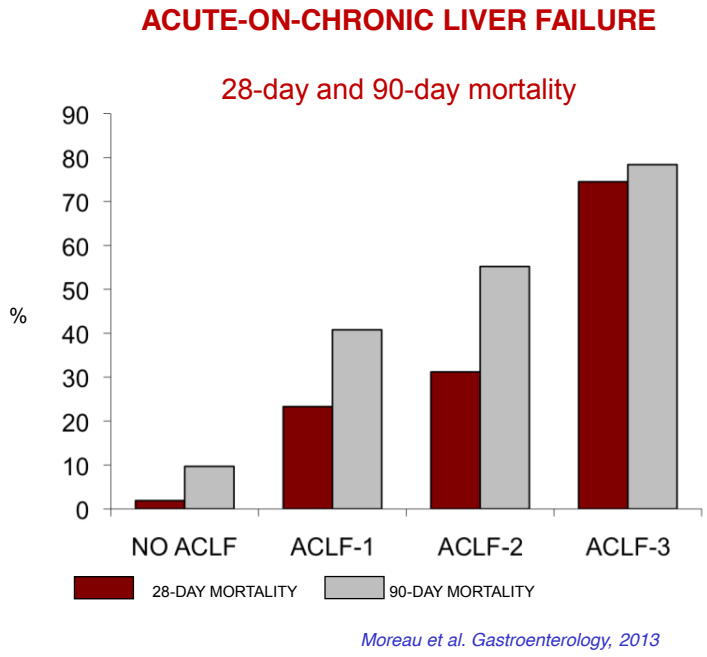


***Figure 8**. 28 and 90 day survival of patients without and with ACLF. Data from the Canonic Study (55)*

1.8 d Management

The management of ACLF is nonspecific and aimed at treating complications as well as managing precipitating events (i.e. alcoholic hepatitis, bacterial infections, etc) and involves intensive care support. Patients with ACLF have been shown to benefit from liver transplantation without increased risk for post-transplant complications compared to non-ACLF patients. Unfortunately, cerebral edema, active infection and hemodynamic instability, commonly present in patients with ACLF, are major contraindications for liver transplant. Therefore, further studies are needed to determine timing of transplantation and whether prioritizing criteria for acute liver failure are also applicable for patients with ACLF.

2. JUSTIFICATION & OBJECTIVES

Hyponatremia is associated with poor outcomes and thus adequate management is of key importance as improvement in serum sodium levels will reduce the need for fluid restriction, may lessen the risk of hepatic encephalopathy and finally it may beneficial in patients with low serum sodium levels awaiting liver transplantation as it may mitigate the risk of neurological and infectious complications after liver transplantation. The proper management of hyponatremia in patients with cirrhosis is very challenging because the available therapies are limited and in most cases ineffective. As described above the use of fluid restriction, administration of sodium chloride and albumin infusions are rarely effective and very impractical. The novel V2 receptor antagonists that block the effects of circulating AVP are effective in raising serum sodium in patients with hypervolemic hyponatremia. Although numerous vaptans have been studied in patients with hypervolemic hyponatremia, problems related to side effects and increased mortality in some studies led to the abandonment of promising drugs such as satavaptan and lixivaptan. Thus the only available pharmacological therapy for hypervolemic hyponatremia is tolvaptan. The safety and efficacy of this drug has been assessed in pivotal studies in patients with hypervolemic hyponatremia and the results show that mean serum sodium levels effectively increase during the first 7 days and are maintained above 130 mEq/L during 1 month. However, in these studies, no evaluation was performed according to the disease responsible for hyponatremia. Thus, there is lack of data on the specific effects of tolvaptan in patients with cirrhosis and hyponatremia.

As described above the presence of hyponatremia is associated with a poor prognosis in patients with advanced cirrhosis. However during the natural history of cirrhotic patients may develop acute decompensations which may be manifested by one or more complications such as the appearance of ascites, hepatic encephalopathy, gastrointestinal bleeding, and/or bacterial infections. These acute events may occur spontaneously, but more commonly appear in relation with different organ failures (i.e. liver, kidney, cerebral, circulatory, and pulmonary or coagulation failures). The recent definition ACLF is based on the type and degree of organ failures which help stratify and determine prognosis for subjects with and without ACLF. Among the variables analyzed as risk factors a high CLIF-SOFA and a high leukocyte count were found to be predictive for the development of ACLF and ACLF associated mortality. However hyponatremia was not as an independent prognostic factor in ACLF. Since hyponatremia has been recognized as a powerful prognostic marker in patients with cirrhosis

without ACLF the question remains as whether low serum sodium levels have an impact on the outcome of patients with ACLF.

The aim of this thesis is to illustrate the safety and efficacy of tolvapan in patients with cirrhosis, ascites and hypervolemic hyponatremia and describe the impact of hyponatremia in patients with ACLF.

Objectives

Study 1 *- Cárdenas A, Ginès P, Marotta P, Czerwiec F, Oyuang J, Guevara M, Afdhal NH. Tolvaptan, an oral vasopressin antagonist, in the treatment of hyponatremia in cirrhosis. J Hepatol. 2012 Mar;56(3):571-8.*

PRIMARY AIM

1. Evaluate the safety and efficacy of tolvaptan in raising serum sodium levels in patients with cirrhosis and ascites in a subanalysis of the SALT -1 and 2 studies.

2. SECONDARY AIM

Evaluate the absolute serum sodium concentrations at each visit and percentage of patients with normalized serum sodium. Other endpoints include changes in fluid intake, change in body weight and changes in components of health related quality of life

Study 2 *- Cárdenas A, Solà E, Rodríguez E, Barreto R, Graupera I, Pavesi M, Saliba F, Welzel T, Martinez-Gonzalez J, Gustot T, Bernardi M, Arroyo V, Ginès P; CANONIC study investigators of the EASL-CLIF Consortium. Hyponatremia influences the outcome of patients with acute-on-chronic liver failure: an analysis of the CANONIC study. Crit Care. 2014 Dec 13;18(6):700.[Epub ahead of print]*

PRIMARY AIM

Determine the specific effects hyponatremia on the outcome of patients with ACLF.

2. SECONDARY AIM:

Evaluate the prevalence, incidence, natural history, and predictive factors of hyponatremia in patients with ACLF.

3. RESULTS

Study 1

Tolvaptan, an oral vasopressin antagonist, in the treatment of hyponatremia in cirrhosis

Cárdenas A, Ginès P, Marotta P, Czerwiec F, Oyuang J, Guevara M, Afdhal NH..

J Hepatol. 2012 Mar; 56 (3):571-8.

Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Tolvaptan, an oral vasopressin antagonist, in the treatment of hyponatremia in cirrhosis

Andrés Cárdenas[1,2,*,†], Pere Ginès[2,3,†], Paul Marotta[4,†], Frank Czerwiec[5,†], John Oyuang[5,†], Mónica Guevara[2,3,†], Nezam H Afdhal[6,†]

[1]*GI Unit, Institut de Malalties Digestives i Metaboliques, Hospital Clínic, University of Barcelona, Barcelona, Catalunya, Spain;* [2]*Institut d'Investigacions Biomèdiques August Pi-Sunyer (IDIBAPS), CIBER de Enfermedades Hepáticas y Digestivas CIBEREHD, Barcelona, Catalunya, Spain;* [3]*Liver Unit, Institut de Malalties Digestives i Metaboliques, Hospital Clinic, University of Barcelona, Barcelona, Catalunya, Spain;* [4]*London Health Sciences Centre, London, Ontario, Canada;* [5]*Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville Maryland, USA;* [6]*Liver Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA*

Background & Aims: Tolvaptan is a vasopressin V2-receptor antagonist that improves serum sodium concentration by increasing renal solute-free water excretion. Specific data on the safety and efficacy of tolvaptan in patients with cirrhosis and hyponatremia has not been exclusively evaluated.

Methods: This sub-analysis of the Study of Ascending Levels of Tolvaptan trials examined cirrhotic patients with hyponatremia who received 15 mg oral tolvaptan (n = 63; increased to 30 or 60 mg if needed) or placebo (n = 57) once-daily for 30 days. At baseline, 44% had mild hyponatremia (serum sodium 130–134 mmol/L), 56% had marked hyponatremia (serum sodium <130 mmol/L), 85% had cirrhosis due to alcohol and/or hepatitis B/C, and 80% were Child-Pugh class B/C.

Results: Tolvaptan was effective in raising serum sodium. Average daily area under the curve for serum sodium was significantly greater in the tolvaptan group from baseline to day 4 (p <0.0001) and day 30 (p <0.0001). This superiority was maintained after stratification by baseline hyponatremia (mild and marked), estimated glomerular filtration rate (⩽60 ml/min and >60 ml/min), or serum creatinine levels (<1.5 mg/dl and ⩾1.5 mg/dl). Hyponatremia recurred 7 days after discontinuation of tolvaptan. Mean mental component summary scores of the SF-12 health survey improved from baseline to day 30 in the tolvaptan group but not the placebo group (4.68 *vs.* 0.08, p = 0.02). Major side effects due to tolvaptan were dry mouth and thirst. Gastrointestinal bleeding occurred in 10% and 2% of patients in the tolvaptan and placebo group, respectively (p = 0.11). Adverse event rates, withdrawals, and deaths were similar in both groups.

Conclusions: One month of tolvaptan therapy improved serum sodium levels and patient-reported health status in cirrhotic patients with hyponatremia. Hyponatremia recurred in tolvaptan-treated patients after discontinuation.

Introduction

Patients with cirrhosis may retain fluids due to an abnormal regulation of extracellular fluid volume leading to increased renal sodium and solute-free water re-absorption. In some patients, excessive solute-free water retention may lead to hyponatremia occurring in the setting of this expanded extracellular fluid volume. This type of hyponatremia is known as dilutional or hypervolemic hyponatremia and usually occurs in patients with advanced cirrhosis [1,2]. In cirrhosis, splanchnic vasodilation secondary to sinusoidal portal hypertension leads to arterial underfilling, which in turn unloads high-pressure baroreceptors that stimulate a non-osmotic hypersecretion of arginine vasopressin (AVP), thereby leading to solute-free water retention and hyponatremia [2,3]. Hyponatremia in cirrhosis has been linked to hepatic encephalopathy, impaired quality of life, and poor short-term prognosis [4,5].

Restricting fluids to 1–1.5 liters per day had been, until recently, the only available method for managing hypervolemic hyponatremia. However, this method has very limited efficacy in improving serum sodium levels [6,7]. Other treatments, such as demeclocycline or urea, are not approved by the Food and Drug Administration (FDA) or by the European Medicines Agency (EMEA), are slow to correct serum sodium, and are potentially nephrotoxic in cirrhosis [8–10]. The administration of hypertonic saline solution is not recommended because additional expansion of the extracellular fluid worsens edema and ascites and, with over-rapid correction, can induce osmotic demyelination [3,6]. Additionally, hypertonic saline solution infusion lacks a

Keywords: Cirrhosis, Dilutional hyponatremia; Ascites; Chronic liver disease; Edema; Vaptans; Antidiuretic hormone; Arginine vasopressin.

Received 27 April 2011; received in revised form 27 July 2011; accepted 15 August 2011; available online 23 October 2011

* Corresponding author. Address: Institut Clinic de Malalties Digestives i Metaboliques, University of Barcelona, Hospital Clinic – Villaroel 170, 08036 Barcelona, Spain. Tel.: +34 93 227 5513; fax: +34 93 227 9850.

E-mail address: acardena@clinic.ub.es (A. Cárdenas).

† For the SALT study investigators.

Abbreviations: ANCOVA, analysis of covariance; AUC, area under the curve; AVP, arginine vasopressin; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; MCS, mental component summary; MDRD-6, modification of diet in renal disease six variable formula; MELD, mean model end-stage liver disease; PCS, physical component summary; SALT, study of ascending levels of tolvaptan in hyponatremia; SF-12 health survey, medical outcomes study 12-item short form general health survey; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

controlled safety database and a consensus on infusion rate. Most importantly, none of the prior therapeutic options addresses the underlying pathophysiology of the hyponatremia, which is related to increased AVP levels.

Oral selective antagonists of AVP that bind to the V2 receptor of the principal cells of the renal collecting ducts are effective in increasing serum sodium levels in hypervolemic hyponatremia [11]. Tolvaptan, an orally active, selective, nonpeptide V2 antagonist, induces the excretion of electrolyte-free water without increasing the total level of electrolyte excretion. This agent is approved for the treatment of dilutional hyponatremia associated with SIADH, cardiac failure or cirrhosis by the FDA in the United States, for SIADH by the EMEA in Europe, and for diuretic-resistant volume overload in heart failure by the Ministry of Health in Japan. Pivotal studies of tolvaptan enrolled patients with hyponatremia due to SIADH, cardiac failure, and cirrhosis have been conducted. The results of these pivotal studies indicate that tolvaptan effectively improves serum sodium levels in these patients [12,13]. In these studies, no evaluation was performed on the disease responsible for hyponatremia. Thus, there is lack of data on the specific effects of tolvaptan in patients with cirrhosis and hyponatremia. Given that tolvaptan is the only oral vaptan approved for management of hyponatremia, its efficacy in the population of patients with cirrhosis is of interest to practicing clinicians. Therefore, the current study reports a sub-analysis of the tolvaptan pivotal studies evaluating the efficacy and safety of tolvaptan in patients with cirrhosis and hyponatremia.

Patients and methods

Patients

This report represents an analysis of patients with cirrhosis enrolled in two prospective, multicenter, randomized, placebo-controlled, double-blind, phase 3 studies (study of ascending levels of tolvaptan in hyponatremia 1 and 2 [SALT1 and SALT2]; Clinicaltrials.gov registration numbers NCT00072683 and NCT00201994). SALT1 and 2 examined the effects of tolvaptan (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) on hypervolemic and euvolemic hyponatremia of diverse etiology, including congestive heart failure (CHF), syndrome of inappropriate antidiuretic hormone secretion (SIADH), and cirrhosis [13]. The study described here includes only those patients in SALT1 and SALT2 with hyponatremia resulting from cirrhosis.

Patients aged 18 years or older, with nonacute hypervolemic hyponatremia due to cirrhosis, were eligible. Patients with hypovolemic hyponatremia were excluded. Patients with ascites underwent a sodium restricted diet of 90 mmol/day and were kept on diuretics at the discretion of the treating physician. Hyponatremia was classified as either mild (baseline serum sodium concentration of 130–134 mmol/L) or marked (baseline serum sodium concentration of <130 mmol/L). Patients with a serum sodium <120 mmol/L were excluded if they had associated significant neurological impairment. Other reasons for exclusion were: severe cardiopulmonary disease; cerebrovascular accident; multiple strokes; systolic blood pressure <90 mmHg; severe pulmonary hypertension; urinary tract obstruction; uncontrolled diabetes mellitus; progressive or episodic neurological disease; or a serum creatinine >3.5 mg/dl (309 μmol per liter). Terminally ill patients with little chance of short-term survival were also excluded.

Study design

SALT1 was conducted between April 11, 2003 and December 20, 2005 at 42 sites in the United States. SALT2 was conducted between November 20, 2003 and July 6, 2005 at 50 international sites. All patients enrolled in the study provided written informed consent. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki [14] as reflected in *a priori* approval by the appropriate institutional review committee.

Eligible patients were centrally randomized using random permuted blocks and stratified according to the severity of their hyponatremia (marked [<130 mmol/L] or mild [130–134 mmol/L]). Patients were randomized in a 1:1 ratio to receive oral tolvaptan or visually identical placebo once daily in the morning for 30 days. Treatment with lithium chloride, demeclocycline, or urea was not permitted. Fluid restriction was at the discretion of the investigator, but generally recommended to be avoided during study drug titration. Hospitalization was required on day 1 only; most patients were discharged by day 4.

On day 1, patients received a 15 mg oral tablet of tolvaptan or matching placebo. Based on the patient's serum sodium and a regimen designed to correct the sodium slowly, the dose of study drug could be increased from 15 to 30 mg and from 30 to 60 mg, during the first 4 days of therapy and at the investigators' discretion throughout the 30-day treatment. If serum sodium was less than 136 mmol/L and had increased by less than 5 mmol/L during the prior 24 h, the dose was increased. If serum sodium concentration exceeded 145 mmol/L, increased by more than 8 mmol/L during 8 h on day 1, or increased by more than 12 mmol/L during 24 h, investigators withheld the next day's dose or increased the patient's fluid intake.

Study assessments

Patients were assessed at baseline, 8 h after the first dose of study drug, and on days 2, 3, 4, 11, 18, 25, 30, and 37. Study drug was stopped at day 31. At day 37, the effect of stopping the study drug on serum sodium was assessed.

The primary endpoints of the SALT 1 and 2 studies were the changes in average daily area under the curve (AUC) of serum sodium concentration from baseline to day 4 and from baseline to day 30. Secondary endpoints included: the absolute serum sodium concentrations at each visit; percentage of patients with normalized serum sodium (>135 mmol/L) at day 4 and day 30; change in AUC for serum sodium concentration in patients with mild and marked hyponatremia; time to normalization of serum sodium concentration; and categorical serum sodium concentrations at day 4 and day 30. Additional secondary endpoints included: changes in fluid intake and output on day 1, change in body weight on day 1, and fluid restriction or use of intravenous saline as rescue therapy. Finally change from baseline to day 30 on the physical component summary (PCS) and mental component summary (MCS) of the medical outcomes study 12-item short form (SF-12) general health survey was recorded [15,16]. We chose the SF-12 health survey for the assessment of overall health status because it has been validated as a broadly applicable instrument measuring health-related quality of life. Clinical outcomes such as effect of ascites resolution, changes in degree of hepatic encephalopathy and changes in renal function were not a focus of this study and were not specifically evaluated.

Adverse events

Adverse events and laboratory abnormalities were monitored throughout the 30 days of the study and the 7-day follow-up period. Patients could spontaneously report adverse events to investigators. Investigators were required to assess the seriousness and severity of each event and the probability of an association between the study drug and the adverse event and to report this information to the sponsor.

Statistical analysis

The two primary end points, the changes in average daily AUC of serum sodium concentration from baseline to day 4 and from baseline to day 30, were calculated as AUC for each patient, divided by the length of the observation period (3 or 30 days) minus the baseline value. Changes in serum sodium AUC and the change in serum sodium concentration in the two treatment groups were compared using an analysis of covariance (ANCOVA) model with treatment group and baseline stratification as factors and baseline serum sodium as covariate. The percentage of patients with normalized serum sodium (>135 mmol/L) and the percentage of patients requiring fluid restriction were analyzed with the Cochran–Mantel–Haenszel test, stratified by baseline stratification factors. Categorical changes in hyponatremia severity were analyzed using the Cochran–Mantel–Haenszel mean score test with a modified Ridit score (van Elteren test). This analysis was performed separately for patients with mild and marked hyponatremia at baseline. Post-treatment categories were normal (135–145 mmol/L), mild, and marked hyponatremia. The time to normalization of the serum sodium concentration was analyzed with the use of a log-rank test. Using an analysis of variance model, with treatment group and baseline stratification as factors, fluid loss, fluid intake, and fluid balance (total intake minus total output) on day 1 was analyzed. Only observed case (OC) data were used for AUC, categorical change and SF-12

analysis, while missing data were imputed using the Last Observation Carried Forward (LOCF) principle for change from baseline analyses. Where post-treatment (i.e. treatment withdrawal) data are considered, an OC data set was used.

We chose the SF-12 health survey for the assessment of overall health status because it has been validated as an instrument of quality of life [15,16]. The physical component summary (PCS) scale of the SF-12 ranges from 5 to 69 and the mental component summary (MCS) scale ranges from 8 to 73. Higher scores indicate better functioning. The physical component evaluates physical functioning, physical limitations on activities, and pain. The mental component evaluates social functioning, vitality, emotional or limited accomplishment, calmness, and sadness. An absolute shift from baseline of three or more units is considered a minimally important clinical difference [16]. Change from baseline was analyzed with an ANCOVA model; covariate was baseline score, and factors were baseline stratification factors and treatment group. Reported *p*-values were 2-sided.

Results

Study patients

The demographic and baseline characteristics of patients in the two treatment groups were similar. Liver and renal function tests, as well as serum sodium concentration at the time of randomization, are shown in Table 1. Sodium levels between 131–135 meq/L are not uncommon in patients with Child A cirrhosis as impairment of solute-free water excretion can develop in those with mild ascites and edema [1,2]. About half of these subjects had mild and half more severe hyponatremia. In those with the lowest sodium levels, it is possible that other factors (concomitant CHF, iatrogenic causes) may have contributed to the severity of hyponatremia. Prior to study treatment, 98% of patients in the tolvaptan group and 100% of patients in the placebo group were taking diuretics (spironolactone and/or furosemide). The majority of patients were on a moderate dose (spironolactone <200 mg/day and furosemide <80 mg/day) (Supplementary Table A). The algorithm of patient disposition is shown in Fig. 1. Forty-eight (72.6%) out of the 63 patients randomized to tolvaptan and 38 (66.7%) out of 57 patients randomized to placebo completed the 30-day study period and the 7-day follow-up.

Table 1. Demographic and clinical characteristics of patients at entry into the study.

	Tolvaptan (n = 63)	Placebo (n = 57)
Age, yr	52 (8)	55 (9)
Female gender, n (%)	13 (20.6)	19 (33.3)
Race, n (%)		
White	55 (87.3)	49 (86.0)
Black	1 (1.6)	2 (3.5)
Hispanic	5 (7.9)	6 (10.5)
Asian	1 (1.6)	0
Other	1 (1.6)	0
Mean weight, kg	78 (23)	76 (19)
Etiology of cirrhosis, n (%)		
Alcoholic	34 (54.0)	30 (52.6)
Hepatitis C	19 (30.2)	15 (26.3)
Cryptogenic	3 (4.8)	5 (8.8)
Hepatitis B	2 (3.2)	2 (3.5)
Other	1 (1.6)	1 (1.8)
MELD score	15.8 (5.0)	16.3 (6.4)
Child-Pugh class, n (%)		
Grade A	11 (17.5)	6 (10.5)
Grade B	33 (52.4)	28 (49.1)
Grade C	16 (25.4)	19 (33.3)
eGFR (MDRD-6) ml/min/1.73 m^2	76.3 (35.4)	67.7 (30.2)
Serum albumin (g/dl)	2.8 (0.7)	2.8 (0.7)
Serum bilirubin (mg/dl)	4.0 (5.6)	3.8 (5.0)
Serum creatinine (mg/dl)	1.0 (0.4)	1.1 (0.6)
Prothrombin time (sec)	15 (1.9)	15 (2.8)
Serum sodium, mmol/L	128.8 (4.3)	128.6 (4.4)
Degree of hyponatremia		
Mild (130–134 mmol/ml), n (%)	28 (44.4)	25 (43.9)
Mean serum sodium, mmol/L	132.4 (1.5)	132.4 (1.1)
Marked (<130 mmol/ml), n (%)	35 (55.6)	32 (56.1)
Mean serum sodium, mmol/L	126.0 (3.6)	125.6 (3.5)

MELD, model end-stage liver disease; SD, standard deviation, eGFR, estimated glomerular filtration rate. Values are mean ± standard deviation (SD) or number and percentages. MDRD-6, modification of diet in renal disease six variable formula.

Effect of treatment on serum sodium concentration

The increase in the average daily AUC for serum sodium was significantly greater in the tolvaptan group than in the placebo group from baseline to day 4 and from baseline to day 30 (Table 2). The increase in the average daily AUC for serum sodium was also significantly greater in the tolvaptan group when patients were categorized according to baseline hyponatremia (mild *vs.* marked), baseline eGFR, or serum creatinine value (Table 2).

Similarly, the absolute change in serum sodium from baseline to day 4 and from baseline to day 30 was significantly greater in the tolvaptan group than in the placebo group (Table 2 [LOCF] and Fig. 2A [OC]). This effect was seen both in the mild and marked hyponatremic patients (Fig. 2B and C [OC]). The statistically significant difference between tolvaptan and placebo in increasing the absolute value of serum sodium from baseline to day 4, and from baseline to day 30 was generally maintained when patients were categorized by baseline hyponatremia, eGFR and serum creatinine. However, the absolute change in serum sodium for tolvaptan versus placebo at day 30 in patients with marked hyponatremia and for those with an eGFR of <60 ml/min did not achieve statistical significance ($p = 0.0840$ and $p = 0.0576$, respectively) (Table 2). This analysis was not significant at day 30 in patients with serum creatinine $\geqslant 1.5$ mg/dl ($p = 0.27$), although only 10 tolvaptan- and 8 placebo-treated subjects were available for this subgroup's analysis. Although not tested for significance of the difference, the nominal changes in serum sodium were greater in those with more severe hyponatremia, but lesser in those with more severe renal insufficiency.

Fluid status during day 1 is shown in Supplementary Table B. Urine output and fluid intake on day 1 was significantly greater in the tolvaptan group, and fluid balance on day 1 was significantly more negative compared to placebo. When patients were stratified by eGFR, the significantly greater negative fluid balance in the tolvaptan group persisted in both the high and low eGFR groups, although a greater net difference in fluid balance was

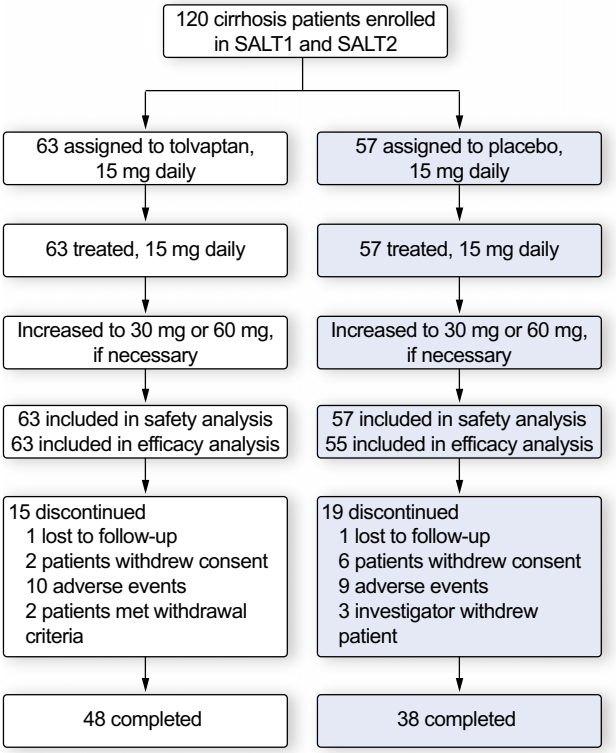


Fig. 1. Progress of patients through the trial.

apparent for those with preserved renal function, as compared with those whose eGFR was <60 ml/min. The percentage of patients on fluid restriction at day 1 was not significantly different between treatment groups, nor was the change in body weight at day 1. No patients required intravenous saline as rescue therapy for hyponatremia.

Responder analyses, based on normalization of serum sodium (>135 mmol/L), were pre-specified using the last observation carried forward principle. The proportion of tolvaptan-treated patients exceeding this threshold at day 4 (72 h after initial dose) was 41%, as compared to 11% for placebo, ($p = 0.0002$). At day 30, these proportions were 33% and 19% ($p = 0.0838$), respectively. Time to normalization (>135 mmol/L) was significantly lower in the tolvaptan group compared to that of the placebo group (hazard ratio = 2.27 [95% CI, 1.343, 3.821; $p = 0.0010$]).

Seven days after study drug withdrawal, using the observed case analyses, the proportions of patients remaining in the normal range reverted. Similarly, the mean serum sodium concentration for the tolvaptan group reverted near to values in the placebo group (Fig. 2).

Effects of treatment on SF-12 health survey

The effect of study drug on a pre-specified analysis of PCS and MCS scores of the SF-12 health survey at day 30 was examined. Mean PCS scores did not improve significantly from their baseline values over the 30-day treatment period in either treatment group (Table 3). However, mean MCS scores showed significant improvement from baseline to day 30 in the tolvaptan group relative to the placebo group (treatment effect = 4.60; $p = 0.0185$)

Table 2. Effects of tolvaptan or placebo on serum sodium concentrations. Values are expressed as change in average area under the curve (AUC) of serum sodium (upper part) or absolute changes in serum sodium (lower part).

Variable	Tolvaptan	Placebo	*p* value
Change in average AUC of serum sodium, mmol/L ± SD			
All patients	n = 63	n = 57	
Day 4	3.5 ± 2.4	0.3 ± 2.3	<0.0001
Day 30	4.2 ± 3.4	1.2 ± 3.5	<0.0001
Mild hyponatremia	n = 28	n = 25	
Day 4	3.1 ± 1.9	-0.2 ± 1.7	<0.0001
Day 30	3.2 ± 3.2	-0.2 ± 2.4	<0.00001
Marked hyponatremia	n = 35	n = 32	
Day 4	3.8 ± 2.7	0.7 ± 2.6	<0.0001
Day 30	4.9 ± 3.4	2.3 ± 3.8	0.003
eGFR >60 ml/min	n = 36	n = 23	
Day 4	3.8 ± 1.9	1.3 ± 2.9	0.0002
Day 30	4.8 ± 3.3	1.6 ± 3.9	0.0009
eGFR ≤60 ml/min	n = 24	n = 34	
Day 4	2.9 ± 2.2	-0.3 ± 1.5	<0.0001
Day 30	3.6 ± 3.3	0.9 ± 3.1	0.001
Scr <1.5 mg/dl	n = 49	n = 46	
Day 4	3.6 ± 2.0	0.5 ± 2.4	<0.0001
Day 30	4.5 ± 3.3	1.4 ± 3.2	<0.0001
Scr ≥1.5 mg/dl	n = 10	n = 8	
Day 4	2.5 ± 1.9	-0.6 ± 1.7	0.0009
Day 30	3.5 ± 3.2	1.1 ± 4.6	0.06
Absolute change in serum sodium, mmol/L ± SD			
All patients	n = 63	n = 57	
Day 4	4.7 ± 4.4	0.3 ± 3.8	<0.0001
Day 30	4.2 ± 4.5	1.3 ± 6.0	0.002
Mild hyponatremia	n = 28	n = 25	
Day 4	3.7 ± 2.9	-0.2 ± 3.4	<0.001
Day 30	3.1 ± 3.9	-0.3 ± 5.0	0.007
Marked hyponatremia	n = 35	n = 32	
Day 4	5.6 ± 5.1	0.8 ± 4.1	<0.001
Day 30	5.0 ± 4.8	2.6 ± 6.4	0.08
eGFR >60 ml/min	n = 36	n = 23	
Day 4	5.1 ± 4.0	1.7 ± 4.5	0.0006
Day 30	5.1 ± 3.8	2.3 ± 6.5	0.04
eGFR ≤60 ml/min	n = 24	n = 34	
Day 4	4.0 ± 3.7	-0.7 ± 2.9	<0.0001
Day 30	3.4 ± 5.0	0.7 ± 5.6	0.057
SCr <1.5 mg/dl	n = 49	n = 46	
Day 4	4.7 ± 3.8	0.70 ± 3.8	<0.0001
Day 30	4.4 ± 4.4	1.5 ± 5.9	0.008
SCr >1.5 mg/dl	n = 10	n = 8	
Day 4	4.4 ± 4.7	-0.5 ± 3.3	0.04
Day 30	4.1 ± 4.4	1.4 ± 5.6	0.27

AUC, area under the concentration curve; eGFR, estimated glomerular filtration rate by MDRD-6; SCr, serum sodium concentration; SD, standard deviation. Missing data are imputed using the last observation carried forward principle.

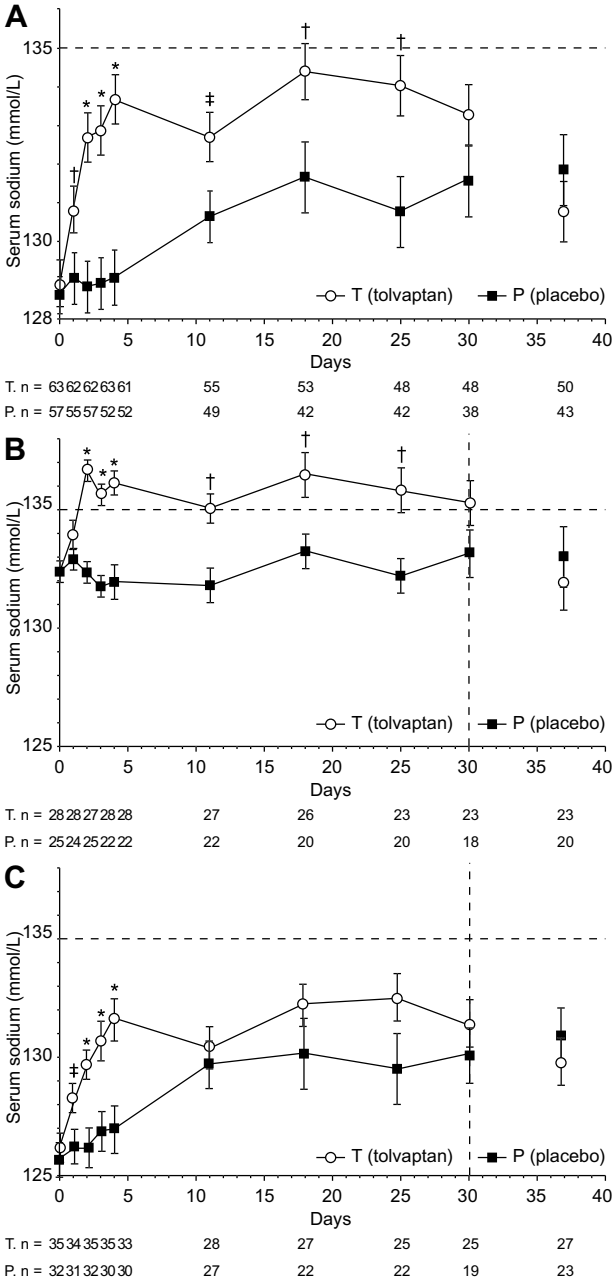


Fig. 2. Observed serum sodium concentration throughout the study treatment period (days 1–30) and 7 days after stopping (day 37) tolvaptan (I) or placebo (P) in (A) all patients, (B) those with mild hyponatremia and (C) those with marked hyponatremia. Error bars are mean ±SE. *p <0.001, tolvaptan *vs.* placebo; †p <0.01, tolvaptan *vs.* placebo; ‡p <0.05, tolvaptan *vs.* placebo.

(Table 3). In addition, the median score subgroup analyses revealed that this difference was significant in the subgroup with mild hyponatremia (treatment effect = 6.33; p = 0.0251). Supplementary Fig. A shows the correlation between the AUC of change from baseline in serum sodium level up to day 30 and change from baseline in the SF-12 MCS score at day 30 or last visit. Those with a change from baseline serum sodium >5 meq/L had the most relevant effect on the MCS.

Table 3. Change from baseline in SF-12 health survey mental component summary (MCS) and physical component summary (PCS) scores.

	MCS score		Treatment effect	p
	Tolvaptan (n)	Placebo (n)		
All patients				
Baseline	43.1 (61)	43.2 (57)		
Day 30	47.7 (53)	43.3 (51)	4.60	0.0185
Mild hyponatremia				
Baseline	42.7 (28)	47.8 (25)		
Day 30	47.1 (25)	44.8 (23)	6.33	0.0251
Marked hyponatremia				
Baseline	43.4 (33)	39.7 (32)		
Day 30	48.3 (28)	42.0 (28)	4.72	0.0952
	PCS score		Treatment effect	p
	Tolvaptan (n)	Placebo (n)		
All patients				
Baseline	31.2 (61)	31.4 (57)		
Day 30	32.1 (53)	31.0 (51)	0.83	0.6232
Mild hyponatremia				
Baseline	32.6 (28)	31.7 (25)		
Day 30	36.5 (25)	32.2 (23)	2.90	0.2850
Marked hyponatremia				
Baseline	30.0 (33)	31.1 (32)		
Day 30	28.2 (28)	30.0 (28)	-1.34	0.4967

MCS, mental component summary; PCS, physical component summary.
All data are from the ITT data set (last observation carried forward). A treatment effect of 0.3 is considered a minimally important difference.

Safety

Overall adverse events occurred in 92.1% of tolvaptan patients and 82.5% of placebo patients. Adverse events, withdrawals, and deaths are shown in Table 4. Treatment-emergent adverse events occurring in more than 5% of patients in either group are shown in Supplementary Table C. The most common treatment-emergent adverse event seen in both groups was ascites, whereas the most common emergent adverse events in the tolvaptan group were thirst, dry mouth, and hyperkalemia.

Treatment-emergent serious adverse events occurred in 38.1% of tolvaptan patients and 29.8% of placebo patients. Treatment-emergent adverse events resulting in discontinuation of study drug occurred in 14.3% and 15.8% of patients in the tolvaptan and placebo group, respectively. The most common disorders resulting in discontinuation were hepatobiliary (hepatic failure in one patient on tolvaptan, hepatorenal syndrome in one patient on placebo, and veno-occlusive liver disease in one patient on placebo), renal and urinary disorders (nocturia in one patient on tolvaptan, acute renal failure in three patients on placebo), and nervous system (hepatic encephalopathy in two patients on tolvaptan, and hepatic encephalopathy in one patient on placebo). Throughout the study, potentially clinically significant increases in serum creatinine (defined as serum creatinine

Table 4. Adverse events, withdrawals, and deaths in the two treatment groups.

	Tolvaptan (n = 63)	Placebo (n = 57)
Total patient-days of drug exposure	1616	1348
Patients with treatment-emergent adverse events, n (%)	58 (92.1)	47 (82.5)
Patients with serious treatment-emergent adverse events, n (%)	24 (38.1)	17 (29.8)
Withdrawals due to adverse events, n (%)	9 (14.3)	9 (15.8)
Deaths, n (%)	5 (7.9)	4 (7.0)

⩾1.5 mg/dl) occurred in 11.7% of patients in the tolvaptan group and 16.1% of patients in the placebo group.

Among the 63 patients in the tolvaptan group, there were four deaths due to treatment-emergent adverse events that started before the 7-day follow-up visit. Among the 57 patients in the placebo group, there were two such deaths. In the tolvaptan group, the deaths were due to hepatic failure, hepatic encephalopathy, and respiratory failure. One additional death occurred in the tolvaptan group due to a cardiac arrest during the 7-day follow-up. The deaths in the placebo group were due to intestinal ischemia and hepatorenal syndrome, each in a single subject. The desirable rate of correction of sodium concentration (<0.5 mmol/L/h) was not exceeded during the first 24 h in any patient. None of the patients in the tolvaptan group or the placebo group developed hypernatremia (serum sodium >145 mmol/L). Fewer patients in the tolvaptan group had potentially clinically significant increases in potassium, heart rate, and blood pressure. Slightly more patients in the tolvaptan group had potentially clinically significant changes in serum bilirubin (>2.0 mg/dl) (65% *vs.* 60%). The two groups had similar changes in creatinine clearance during the study. Acute increases in serum creatinine can indicate AKI (⩾0.3 mg/dl in first 7 days of treatment); similar proportions of tolvaptan and placebo patients met this criteria (27% *vs.* 26%, $p = 0.83$).

Gastrointestinal bleeding events occurred in six out of 63 (10%) patients receiving tolvaptan and in one out of 57 (2%) patients on placebo ($p = 0.11$). Among patients receiving tolvaptan, five had evidence of upper gastrointestinal hemorrhage and concomitant esophageal varices and one patient had a self-limited episode of bright red blood per rectum attributed to hemorrhoids. The patient on placebo who bled had a gingival hemorrhage and concomitant esophageal varices that were not considered as the cause of hemorrhage. No deaths related to gastrointestinal bleeding occurred in either group.

Discussion

The results of this analysis of the SALT studies indicate that use of the oral vasopressin V2 receptor antagonist tolvaptan for 30 days increases serum sodium concentration in hyponatremic patients with cirrhosis. The administration of tolvaptan was also associated with a significant increase in urine output and fluid intake and a negative fluid balance 24 h after the initial dose when compared to placebo, as well as a significant improvement in the SF-12 health survey MCS scores at day 30. Finally, serum sodium levels reverted to baseline levels after discontinuation of tolvaptan. This analysis is unique in the sense that it specifically evaluates, in cirrhotic patients, the safety and efficacy of the only approved oral vaptan for hyponatremia in this population.

In the current study, tolvaptan was superior to placebo in the increase in the average daily AUC for serum sodium concentrations from baseline to day 4 and from baseline to day 30. It was also superior to placebo when serum sodium levels were measured at follow up in each visit. The absolute value of serum sodium was higher in the tolvaptan group compared to the placebo group from baseline to day 4 and from baseline to day 30. Tolvaptan was superior to placebo in raising serum sodium levels at all time points from day 1 to day 30 and brought more patients into the normal range more quickly. However, in patients with marked hyponatremia in the placebo group, serum sodium levels tended to increase towards the end of therapy but were still lower than in the placebo group at day 30. Both the increase in serum sodium levels while on drug and the drop of serum sodium levels after stopping tolvaptan indicate that V2 receptor antagonism in patients with cirrhosis leads to solute-free water excretion and improvement of serum sodium levels. Previous studies indicated that the use of other V2 receptor antagonists in patients with cirrhosis, ascites, and hypervolemic hyponatremia is efficacious in improving serum sodium levels [7,17–19]. In addition, other studies have shown reduction in body weight probably due to a decrease in ascites and edema [17,20]. The current study was performed for a longer period of time than previous studies with similar results and indicates that the initial response to tolvaptan could occur regardless of the baseline serum sodium level and be maintained throughout the 30 days.

An important finding in this study was the effect of tolvaptan in patients with renal insufficiency. Patients with cirrhosis and hypervolemic hyponatremia are at an advanced stage, with a significant proportion of patients having reduced GFR and elevated serum creatinine levels (>1.5 mg/dl). Renal insufficiency in cirrhosis is due in most cases to renal vasoconstriction, either from hepatorenal syndrome or secondary to bacterial infections. This group of patients usually does not tolerate diuretics well, and in most cases these drugs have to be stopped. However, in the current analysis, diuretics did not influence the treatment with tolvaptan as the majority of patients were on a moderate dose (spironolactone <200 mg/day or furosemide <80 mg/day) and only 6% stopped them during treatment. In the study, the primary endpoint of change in average AUC and absolute change in serum sodium at 30 days, in the group of patients with serum creatinine >1.5 mg/dl, did not reach statistical significance, probably due to the small sample size. Despite the lack of a deleterious effect of treatment with tolvaptan on renal function, it is advisable to monitor serum creatinine at regular and close intervals when patients receive tolvaptan.

The proportion of patients on tolvaptan who normalized serum sodium (>135 mmol/L) at day 4 was 41%, as compared to 11% for placebo. On day 30, these proportions were 33% and 19%, respectively. Although >50% did not achieve normalization in the tolvaptan group, the proportions were still >3-fold and 1.5-fold greater than placebo. The difficulty in achieving near normal sodium levels in the majority of subjects with cirrhosis was also observed in studies of conivaptan (Vaprisol®, YM087), lixivaptan (VPA-985), and satavaptan (SR121463) [17,19,21]. This

suggests that AVP-V2R or AVP-V1/V2R antagonism addresses only part of the underlying pathophysiology of hypervolemic hyponatremia in cirrhosis.

The administration of tolvaptan in this study was safe, with no apparent differences in the development of significant adverse events when compared to the placebo group. Side effects seen more frequently in those patients treated with tolvaptan compared to placebo included dry mouth and thirst, all attributable to the intrinsic and desired effect of tolvaptan on free-water clearance. An infrequent yet important adverse event was a higher number of patients with gastrointestinal bleeding in the tolvaptan group. Six patients in the tolvaptan group and one in the placebo group developed gastrointestinal bleeding. The underlying source of bleeding was likely related to portal hypertension and esophageal varices, but was unclear in the event descriptions. No data on putative mechanisms by which tolvaptan might increase risk for variceal bleeding yet exist. Whether this represents a true effect of treatment will require additional studies and post-market surveillance.

The current use of tolvaptan in hyponatremia mandates administration of the first dose in a hospital setting for close monitoring of serum sodium. The doses should be titrated based on the patient's serum sodium concentration response, with an initial targeted increase of approximately 5 mmol/L, but no greater than 8–12 mmol/L/day to avoid neurological complications, most importantly osmotic demyelination or central pontine myelinolysis. However, these complications have not been reported with the use of V2 receptor antagonists. In the cirrhotic sub-population of the SALT studies, 3 subjects on tolvaptan and 1 on placebo increased by $\geqslant$8 mmol/L in the first 8 h of treatment. No overly rapid increases in serum sodium concentrations ($\geqslant$12 mmol/L per 24 h) were observed in the tolvaptan-treated group, however, in one subject in the placebo group, the concentration increased by 12 mmol on the first day. Additionally, the development of hypernatremia (serum sodium concentration >145 mmol/L) due to increased solute-free water excretion not compensated by water intake did not occur. These potential risks of treatment did not occur in the present study and they have not appeared to be a problem in other studies using vasopressin V2 receptor antagonists in patients with cirrhosis and ascites [7,17,19].

An interesting effect seen in this population was the improvement in health-related quality of life, as determined by the nearly 5-point increase in the MCS score of the SF-12. This change from an abnormal score of 43 to a score of 47.7, which is near the norm of 50 for the US population, would be considered a moderate but clinically significant change [15,16]. Nonetheless, other clinical effects were not evaluated in the current study since the primary endpoints were the changes in serum sodium levels from baseline to day 4 and from baseline to day 30. Therefore, clinical outcomes such as ascites resolution, and changes in the degree of hepatic encephalopathy were not prospectively assessed during the study.

Although the administration of tolvaptan was effective when given for one month, its long-term effects in patients with cirrhosis have not been extensively evaluated. Data from a long-term multicenter open label extension study of the SALT1 and two studies indicates that prolonged tolvaptan maintains increased serum sodium levels with an acceptable safety profile [22]. However, in this long-term study, only 20 patients with cirrhosis were included. Larger randomized placebo controlled studies are needed in order to understand the efficacy and safety of long-term tolvaptan in patients with cirrhosis and hyponatremia.

In summary, the results of this study demonstrate that the administration of tolvaptan in addition to standard therapy, for 1 month, in patients with cirrhosis and hyponatremia, is effective in raising and maintaining serum sodium concentrations. Associated with tolvaptan increase in serum sodium were beneficial effects on early fluid balance and 30-day mental component score of quality of life, in a patient population with a subnormal baseline score. Vaptans significantly improved serum sodium levels and health-related quality of life in patients with cirrhosis and mild hyponatremia. In those with marked hyponatremia and renal failure, there was a trend of improvement of serum sodium levels but, given the limited number of patients, more studies are warranted to evaluate the efficacy of tolvaptan in patients with advanced cirrhosis, renal failure and marked hyponatremia. Although tolvaptan had an as yet unexplained higher incidence of gastrointestinal bleeding compared to placebo, other side effects were comparable to those observed in placebo-treated patients. These findings indicate that the use of tolvaptan warrants further long-term studies to evaluate its safety and efficacy in patients with cirrhosis and hyponatremia.

Conflict of interest

Andrés Cárdenas is a consultant for Otsuka Pharmaceuticals, Orphan Therapeutics and GlaxoSmithKline. Pere Ginès is a consultant for Otsuka Pharmaceuticals, Ferring International, Ikaria Pharmaceuticals, and Novashunt AG. Frank Czerwiec and John Ouyang are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. Nezam Afdhal is an Investigator for Otsuka Pharmaceuticals. Paul Marotta was an investigator for Otsuka. Mónica Guevara has no conflicts of interest to disclose. CIBEREHD is funded by the Instituto Carlos III in Spain.

Writing assistance

Anne Sexton, MD (Independent Contractor with Otsuka), assisted in clinical data preparation and review. David Norris, Ph.D. (Ecosse Medical Communications, LLC, Princeton, NJ, USA), provided editorial assistance during the preparation of the manuscript.

Financial support

This work was sponsored and supported by Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville Maryland, USA.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jhep.2011.08.020.

References

[1] Ginès P, Berl T, Bernardi M, Bichet DG, Hamon G, Jimenez W, et al. Hyponatremia in cirrhosis: from pathogenesis to treatment. Hepatology 1998;28:851–864.

[2] Cárdenas A, Ginès P. Sodium balance in cirrhosis. In: Burnier M, editor. Sodium in Health and Disease. New York: Informa Healthcare; 2008. p. 317–332.
[3] Ginès P, Guevara M. Hyponatremia in cirrhosis: pathogenesis, clinical significance, and management. Hepatology 2008;48:1002–1010.
[4] Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008;359:1018–1026.
[5] Guevara M, Baccaro ME, Torre A, Gomez-Anson B, Rios J, Torres F, et al. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analysis. Am J Gastroenterol 2009;104:1382–1389.
[6] Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. Am J Med 2007;120:S1–21.
[7] Gerbes AL, Gulberg V, Ginès P, Decaux G, Gross P, Gandjini H, et al. Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: a randomized double-blind multicenter trial. Gastroenterology 2003;124:933–939.
[8] Troyer A, Pilloy W, Broeckaert I, Demanet JC. Letter: demeclocycline treatment of water retention in cirrhosis. Ann Intern Med 1976;85:336–337.
[9] Carrilho F, Bosch J, Arroyo V, Mas A, Viver J, Rodes J. Renal failure associated with demeclocycline in cirrhosis. Ann Intern Med 1977;87:195–197.
[10] Decaux G, Mols P, Cauchie P, Flamion B, Delwiche F. Treatment of hyponatremic cirrhosis with ascites resistant to diuretics by urea. Nephron 1986;44:337–343.
[11] Decaux G, Soupart A, Vassart G. Non-peptide arginine–vasopressin antagonists: the vaptans. Lancet 2008;371:1624–1632.
[12] Konstam MA, Gheorghiade M, Burnett Jr JC, Grinfeld L, Maggioni AP, Swedberg K, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 2007;297:1319–1331.
[13] Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 2006;355:2099–2112.
[14] World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects, 2008.
[15] Ware Jr J, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220–233.
[16] Ware JE, Kosinski M, Keller SD. SF-12®: how to score the SF-12® physical and mental health summary scales. 2nd ed. Boston, MA: The Health Institute, New England Medical Center; 1995.
[17] Ginès 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 2008;48:204–213.
[18] Thuluvath PJ, Maheshwari A, Wong F, Yoo HW, Schrier RW, Parikh C, et al. Oral V2 receptor antagonist (RWJ-351647) in patients with cirrhosis and ascites: a randomized, double-blind, placebo-controlled, single ascending dose study. Aliment Pharmacol Ther 2006;24:973–982.
[19] 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 2003;37:182–191.
[20] Okita K, Sakaida I, Okada M, Kaneko A, Chayama K, Kato M, et al. A multicenter, open-label, dose-ranging study to exploratively evaluate the efficacy, safety, and dose-response of tolvaptan in patients with decompensated liver cirrhosis. J Gastroenterol 2010;45:979–987.
[21] O'Leary JG, Davis GL. Conivaptan increases serum sodium in hyponatremic patients with end-stage liver disease. Liver Transpl 2009;15:1325–1329.
[22] Berl T, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, et al. Oral tolvaptan is safe and effective in chronic hyponatremia. J Am Soc Nephrol 2010;21:705–712.

Study 2

Hyponatremia influences the outcome of patients with acute-on-chronic liver failure: an analysis of the CANONIC study

Cárdenas A, Solà E, Rodríguez E, Barreto R, Graupera I, Pavesi M, Saliba F, Welzel T, Martinez-Gonzalez J, Gustot T, Bernardi M, Arroyo V, Ginès P; CANONIC study investigators of the EASL-CLIF Consortium..

Crit Care. 2014 Dec 13; 18 (6):700.[Epub ahead of print]

CRITICAL CARE

RESEARCH Open Access

Hyponatremia influences the outcome of patients with acute-on-chronic liver failure: an analysis of the CANONIC study

Andrs Crdenas [1], Elsa Sol [2], Ezequiel Rodrguez [2], Rogelio Barreto[2], Isabel Graupera[2], Marco Pavesi[3], Faouzi Saliba[4], Tania Mara Welzel[5], Javier Martinez-Gonzalez[6], Thierry Gustot[7], Mauro Bernardi[8], Vicente Arroyo[2], Pere Gins [2,9*] and on behalf of the CANONIC study investigators of the EASL-CLIF Consortium

Abstract

Introduction: Hyponatremia is a marker of poor prognosis in patients with cirrhosis. This analysis aimed to assess if hyponatremia also has prognostic value in patients with acute-on-chronic liver failure (ACLF), a syndrome characterized by acute decompensation of cirrhosis, organ failure(s) and high short-term mortality.

Methods: We performed an analysis of the Chronic Liver Failure Consortium CANONIC database in 1,341 consecutive patients admitted to 29 European centers with acute decompensation of cirrhosis (including ascites, gastrointestinal bleeding, hepatic encephalopathy, or bacterial infections, or any combination of these), both with and without associated ACLF (301 and 1,040 respectively).

Results: Of the 301 patients with ACLF, 24.3% had hyponatremia at inclusion compared to 12.3% of 1,040 patients without ACLF (P <0.001). Model for end-stage liver disease, Child-Pugh and chronic liver failure-SOFA scores were significantly higher in patients with ACLF and hyponatremia compared to those without hyponatremia. The presence of hyponatremia (at inclusion or during hospitalization) was a predictive factor of survival both in patients with and without ACLF. The presence of hyponatremia and ACLF was found to have an independent effect on 90-day survival after adjusting for the potential confounders. Hyponatremia in non-ACLF patients nearly doubled the risk (hazard ratio (HR) 1.81 (1.33 to 2.47)) of dying at 90 days. However, when considering patients with both factors (ACLF and hyponatremia) the relative risk of dying at 90 days was significantly higher (HR 6.85 (3.85 to 12.19) than for patients without both factors. Patients with hyponatremia and ACLF had a three-month transplant-free survival of only 35.8% compared to 58.7% in those with ACLF without hyponatremia (P <0.001).

Conclusions: The presence of hyponatremia is an independent predictive factor of survival in patients with ACLF. In cirrhosis, outcome of patients with ACLF is dependent on its association with hyponatremia.

Introduction

Patients with advanced cirrhosis commonly develop a functional renal impairment that render the kidney susceptible to retain sodium and solute-free water. In some patients, there is disproportionate retention of water relative to sodium, which leads to a dilutional state where water is retained out of proportion to sodium causing hyponatremia and hypoosmolality. Although hyponatremia in patients without end-stage liver disease is defined by serum sodium concentration <135 mEq/L, in cirrhosis it is defined as a serum sodium concentration of less than 130 mEq/L in the presence of ascites or edema [1-3]. In the majority of patients hyponatremia occurs in close association with an impairment of renal function and correlates with poor prognosis. In patients with cirrhosis and ascites, the five-year probability of developing hyponatremia is 37% with a 25% probability of survival at one year [4]. Hyponatremia is also an important marker of prognosis in patients with cirrhosis awaiting liver transplantation

* Correspondence: pgines@clinic.ub.es
[2]Liver Unit, Hospital Clinic, University of Barcelona, Carrer Villarroel, 170, 08036 Barcelona, Spain
[9]University of Barcelona, IDIBAPS, CIBEReHD, IRSIN, Carrer Villarroel, 170, 08036 Barcelona, Catalunya, Spain
Full list of author information is available at the end of the article

and may be associated with an increased morbidity, particularly neurological complications, and reduced survival after transplantation [5-10].

Despite the fact that there is ample data on the relationship and clinical outcomes between serum sodium, hyponatremia, and decompensated cirrhosis, there is no specific information on the frequency, characteristics, and clinical impact of hyponatremia in patients with acute-on-chronic liver failure (ACLF). ACLF is considered a syndrome that occurs in patients with chronic liver disease, with or without previously diagnosed cirrhosis, which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the international normalized ratio (INR)) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to three months from onset [11,12]. The chronic liver failure (CLIF) consortium recently refined the definition of ACLF on the basis of a large prospective, multicenter, observational study [13]. In the study, the overall prevalence of ACLF was 30.9% with a 90-day mortality rate of 49% [13]. Among the many variables analyzed as risk factors in relation to the six organ systems (liver, kidney, brain, coagulation, circulation and lungs) included in the modified sequential organ failure assessment (SOFA) score (CLIF-SOFA), ascites, and a high leukocyte count were found to be predictive for the development of ACLF and ACLF-associated mortality. Serum sodium or hyponatremia were independent variables that did not make it into the definition. Serum sodium (but not hyponatremia) has been included as a mortality predictor in a CLIF-Consortium score derived to predict mortality in patients with and without ACLF (CLIF-C- ACLF score) [14]. Despite these findings it is not well known if the presence of hyponatremia, a strong prognostic factor in patients with cirrhosis, influences the outcome of patients with ACLF. Therefore the aim of this analysis was to determine the specific effects of hyponatremia on the outcome of patients with ACLF.

Methods

Study population and data collection

This report represents an analysis of patients enroled in the Acute-on-Chronic Liver Failure (ACLF) in Cirrhosis (CANONIC) study from the CLIF consortium, which defined specific criteria for ACLF in cirrhosis [13]. ACLF was defined as an acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR) and one or more extrahepatic organ failures in patients with chronic liver disease with or without previously diagnosed cirrhosis. In the CANONIC study, patients with cirrhosis hospitalized with an acute decompensation (AD) (ascites, gastrointestinal bleeding, hepatic encephalopathy, or bacterial infections, or any combination of these) were screened and enroled from February to September 2011 in twenty-nine University Hospitals from eight European countries. A separate Institutional Review Board approval was obtained from the original study sites (see link available at the end of the manuscript, which includes all the International Review Boards that approved the study at the various centers involved). Written informed consent was obtained from patients or their legal surrogates before inclusion. Data regarding history (including previous episodes of AD), physical examination, laboratory tests, and potential precipitating factors of ACLF were recorded. Potential precipitating factors included active alcoholism, gastrointestinal hemorrhage, bacterial infection, therapeutic paracentesis without use of intravenous albumin, transjugular intrahepatic portosystemic shunting, major surgery, and acute hepatitis.

Patients with cirrhosis admitted to the hospital with an AD were enroled in the CANONIC study according to the definition criteria of ACLF. Patients with two or more organ/system failures or those with a single renal failure (serum creatinin ≥ 2 mg/dL) or one or other organ/system failure in combination with renal insufficiency (serum creatinine between 1.5 and 1.9 mg/dL) or a 1 to 2 hepatic encephalopathy grade (West Haven scale) were found to have a poor short-term prognosis and were consequently assumed to present an ACLF episode [13].

Although hyponatremia in the general population is defined as a serum sodium ≤135 mEq/L, in cirrhosis current guidelines and consensus define it as a serum sodium level <130 mEq/L [1,2]. Thus, in this analysis hyponatremia was defined as a serum sodium level <130 mEq/L. Patients with hyponatremia at inclusion or who developed it during hospitalization were managed with fluid restriction between 1 to 1.5 liters per day according to current guidelines [2].

Statistical analysis

Data were summarized by means of the appropriate descriptive statistics (means and standard deviation (SD) for continuous variables, frequencies and percentages for categorical parameters). Univariate analyses included Student s t test or Mann-Whitney U test for parametric or nonparametric pairwise comparisons, respectively, and chi-square tests for categorical variables. Survival curves were estimated by means of the Kaplan-Meier method and compared through the log-rank test. The main study objective was that of assessing the relationship of ACLF and hyponatremia (and their combination) with 90-day mortality. Those risk factors showing a significant association with both ACLF and the presence of hyponatremia were taken into account as potential confounders to adjust the effect of ACLF and hyponatremia on 90-day mortality. Baseline variables associated with ACLF, hyponatremia, and 90-day mortality (that is serum creatinine,

serum bilirubin or INR) were already included in the definition of ACLF, so they were not considered as potential confounders in the multivariate modeling. A proportional hazards model adjusting for these potential confounders and considering liver transplantation as a competing risk was fitted to assess the interaction between ACLF and hyponatremia. A statistically significant interaction (P <0.05) would lead to estimation of the effect of ACLF on mortality separately for each subset of patients with or without hyponatremia. In the absence of a significant interaction, the combination of the independent effects of ACLF and hyponatremia could be estimated through the model. Potential confounders were kept in the final model to adjust the combined effect of hyponatremia and ACLF only if they led at least to a 10% change in model coefficients estimated for the two main factors and their interaction. In all statistical comparisons, a 0.05 significance level (two-tailed) was assumed.

Results

Characteristics of the study population

The prevalence of hyponatremia in patients with and without ACLF is summarized in Figure 1. Mean serum sodium concentration in patients with hyponatremia was 125 4 mEq/L compared to 137 4 mEq/L in patients without hyponatremia (P <0.001). Patients with hyponatremia had higher frequency of bacterial infections, ascites, and hepatic encephalopathy at admission. Moreover, patients with hyponatremia showed signs of more advanced cirrhosis compared to patients without hyponatremia and, in addition, leukocyte count and C-reactive protein (CRP) levels were also higher in patients with hyponatremia (Table 1).

Relationship between hyponatremia and acute-on-chronic liver failure

ACLF was more prevalent in patients with hyponatremia (36.6% vs 20%, P <0.001) (Table 1). When patients with ACLF at inclusion were categorized according to presence or absence of hyponatremia those with hyponatremia and ACLF showed a greater impairment of liver tests (serum bilirubin and aspartate transaminase (AST) levels), higher serum creatinine, higher potassium levels, and higher model for end-stage liver disease (MELD) and Child-Pugh scores than their nonhyponatremic counterparts (Table 2). Moreover, CLIF-SOFA score, a score that evaluates the severity of cirrhosis by assessing the function of six different organs and correlates with prognosis [15], was higher in patients with ACLF and hyponatremia compared to those with ACLF without hyponatremia. Interestingly, leukocyte count was higher in patients with hyponatremia compared to that of patients without hyponatremia, despite a similar frequency of bacterial infections in the two groups (Table 2). In fact, while differences of leukocyte count in infected patients with or without hyponatremia were not significantly different, patients with hyponatremia without bacterial infection (n = 46) had significantly higher leukocyte count than patients without hyponatremia (n = 156) without bacterial infection (11,300 5,700 vs. 8,800 5,000, respectively, P = 0.0062).

Effects of hyponatremia and ACLF on survival

At 90 days of follow-up, 264 of the 1,341 patients had died (19.7%), 961 (71.7%) were alive and 116 (8.7%) had been transplanted. The presence of hyponatremia (either at inclusion or during hospitalization) was a predictive factor of survival both in patients with and without ACLF.

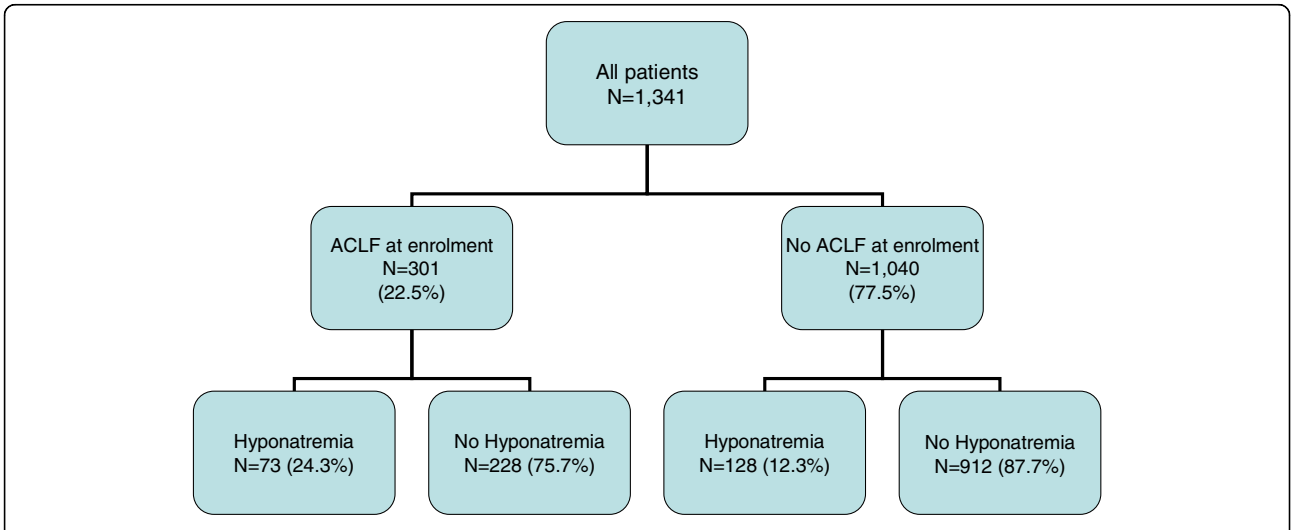


Figure 1 Algorithm of all patients enroled and categorized by the presence of acute-on-chronic liver failure (ACLF) at inclusion and the subsequent development of hyponatremia after inclusion.

Table 1 Characteristics of all patients according to presence of hyponatremia at study enrolment

Patients characteristics	Patients without hyponatremia (Na > = 130 mEq/L) (N = 1140)	Patients with hyponatremia (Na <130 mEq/L) (N = 201)	*P* value
Age (years)	57.2 (12.3)	56.7 (11.5)	0.60
Male sex	724 (63.5)	125 (62.2)	0.72
Alcoholic cirrhosis	550 (48)	108 (53)	0.17
Previous decompensations*	794 (72.6)	149 (77.6)	0.15
*Complications at admission***			
Bacterial infections	264 (23.2)	60 (29.9)	0.04
Hepatic encephalopathy	373 (32.7)	86 (43.0)	0.005
Ascites	738 (65.1)	154 (77.4)	<0.001
Gastrointestinal bleeding	208 (18.3)	13 (6.5)	<0.001
ACLF	228 (20%)	73 (36.3%)	<0.001
Clinical and laboratory data			
Mean arterial pressure (mm/Hg)	84 (12.3)	80 (11.9)	<0.001
Heart rate (beats/min)	81 (16.2)	84 (16.3)	0.02
Serum bilirubin (mg/dL)	5.7 (7.4)	9.2 (9.5)	<0.001
International normalized ratio	1.6 (0.6)	1.8 (0.7)	<0.001
AST (U/L)	96 (158)	153 (282)	0.01
ALT (U/L)	56 (129)	71 (110)	0.12
GGT (U/L)	168 (278)	176 (240)	0.69
Serum creatinine (mg/dL)	1.2 (0.9)	1.7 (1.4)	<0.001
Serum sodium (mEq/L)	137 (4.1)	125 (4.3)	<0.001
Serum potassium (mEq/L)	4.1 (0.7)	4.5 (0.9)	<0.001
Leukocyte count (10^9 cells/L)	7.1 (4.6)	10.1 (6.0)	<0.001
Plasma C-reactive protein (mg/L)	29.9 (36.7)	36.4 (32.0)	0.03
MELD score	18.0 (7.1)	22.6 (8.3)	<0.001
Child-Pugh score	9.5 (2.1)	10.7 (2.1)	<0.001

Data are means (standard deviation (SD)) or number of patients (%). *In the three months prior to study inclusion; **between hospital admission and study inclusion. ACLF: acute-on-chronic liver failure; AST: aspartate transaminase; ALT: alanine transaminase; GGT: gamma-glutamyl transferase; MELD: model for end-stage liver disease.

Several factors measured at study enrolment were associated with both hyponatremia and/or ACLF (Tables 1 and 2) and, at the same time, some were found to be predictors of 90-day mortality: age, presence of ascites and bacterial infections, mean arterial pressure, heart rate, serum potassium and white cell count. All these variables were taken into account as potential confounders for adjusted estimates of the effects of ACLF and hyponatremia on mortality.

The competing-risks proportional hazards model was first fitted including all the potential confounders selected in the univariate analyses, hyponatremia, ACLF and the interaction of the two main factors (Table 3). The interaction between hyponatremia and ACLF was not statistically significant ($P = 0.53$), thus the effects of hyponatremia and ACLF were assumed as independent and adjusted for the potential confounders in order to obtain the final model estimates. After adjusting for confounding variables, hyponatremia without ACLF was found to nearly double the risk of dying at 90 days, while for patients with both ACLF and hyponatremia the relative risk was nearly seven times higher than for patients without either factor (Table 3). The corresponding survival curves of patients with and without ACLF according to the presence of hyponatremia at inclusion are shown in Figure 2. In patients without ACLF, the presence of hyponatremia was associated with a poor prognosis. In fact, patients with hyponatremia without ACLF had a 90-day survival probability of 70.5% compared to 88.9% in patients without ACLF and without hyponatremia (P <0.001). Moreover, the presence of hyponatremia was associated with even a poorer prognosis in patients with ACLF. Patients with ACLF without hyponatremia had a 90-day survival probability of 58.7%, compared

Table 2 Characteristics of patients with acute-on-chronic liver failure (ACLF) according to presence of hyponatremia at study inclusion

Patients characteristics	Patients without hyponatremia (Na > = 130 mEq/L) (N = 228)	Patients with hyponatremia (Na <130 mEq/L) (N = 73)	*P* value
Age (years)	56.1 (11.5)	53.7 (11.4)	0.12
Male sex	148 (64.9)	45 (61.6)	0.61
Alcoholic cirrhosis	136 (59.6)	39 (53.4)	0.54
Previous decompensations*	161 (74.9)	56 (82.4)	0.20
*Complications at admission***			
Bacterial infections	72 (31.9)	27 (37.0)	0.42
Hepatic encephalopathy	130 (57.0)	44 (61.1)	0.54
Ascites	173 (76.2)	61 (85.9)	0.08
Gastrointestinal bleeding	36 (15.8)	5 (6.9)	0.05
Clinical and laboratory data			
Mean arterial pressure (mm/Hg)	79.7 (13.0)	77.3 (12.1)	0.15
Heart rate (beats/min)	83.5 (19.0)	83.3 (16.8)	0.94
Serum bilirubin (mg/dL)	11.0 (11.2)	14.6 (11.3)	0.02
International normalized ratio	2.1 (0.9)	2.1 (0.9)	0.90
AST (U/L)	116 (198)	233 (412)	0.03
ALT (U/L)	57 (98)	95(165)	0.10
GGT (U/L)	139 (151)	153 (194)	0.62
Serum creatinine (mg/dL)	2.2 (1.5)	2.8 (1.9)	0.01
Serum sodium (mEq/L)	136 (4.6)	125 (3.5)	<0.001
Serum potassium (mEq/L)	4.2 (0.8)	4.7 (1.1)	<0.001
Leukocyte count (10^9 cells/L)	9.5 (6.1)	12.1 (7.0)	0.003
Plasma C-reactive protein (mg/L)	40.9 (44.3)	42.0 (36.2)	0.86
MELD score	26.6 (7.0)	30.0 (6.6)	<0.001
Child-Pugh score	10.9 (2.1)	11.6 (2.1)	0.0341
CLIF-SOFA score***	10.1 (3.3)	11.6 (3.1)	0.0034

Data are means (standard deviation (SD)) or number of patients (%). *In the three months prior to study inclusion; **between hospital admission and study inclusion; ***CLIF-SOFA: a score that evaluates the severity of cirrhosis by assessing function of six different organs and correlates with prognosis. See reference [13]. AST: aspartate transaminase; ALT: alanine transaminase; GGT: gamma-glutamyl transferase; MELD: model for end-stage liver disease; CLIF-SOFA: chronic liver failure-sequential organ failure assessment.

to only 35.8% in patients with ACLF and hyponatremia ($P = 0.001$). Similar differences in survival were observed when both patients with hyponatremia at inclusion and during hospitalization were considered (Figure S1 in Additional file 1).

Discussion

This study represents an extensive assessment of the influence of hyponatremia in patients with ACLF. ACLF is considered a distinct entity apart from decompensated cirrhosis; it is defined as an abrupt hepatic deterioration

Table 3 Assessment of the interaction between acute-on-chronic liver failure (ACLF) and hyponatremia at inclusion and estimation of the risk of 90-day mortality adjusted by potential confounding factors

Assessment of ACLF-by-hyponatremia interaction			Estimate of the independent effect of ACLF and hyponatremia		
Parameter	**Hazard ratio (95% CI)***	***P* value**	**Parameter**	**Hazard ratio (95% CI)***	***P* value**
ACLF at study enrolment	3.99 (2.92-5.44)	<0.001	ACLF at study enrolment	3.78 (2.90-4.93)	<0.0001
Hyponatremia at study enrolment	2.00 (1.33-3.02)	0.001	Hyponatremia at study enrolment	1.81 (1.33-2.47)	0.0002
			Combination of independent effects:		
Interaction ACLF-by-hyponatremia	0.83 (0.47-1.48)	0.5300	ACLF/hyponatremia vs. no ACLF/no hyponatremia	6.85 (3.85-12.19)	<0.0001

*Hazard ratio estimates from a competing-risks proportional hazards model, adjusting for age, presence of ascites, presence of bacterial infections, white cell count, heart rate and serum potassium at study enrolment. CI: confidence interval.

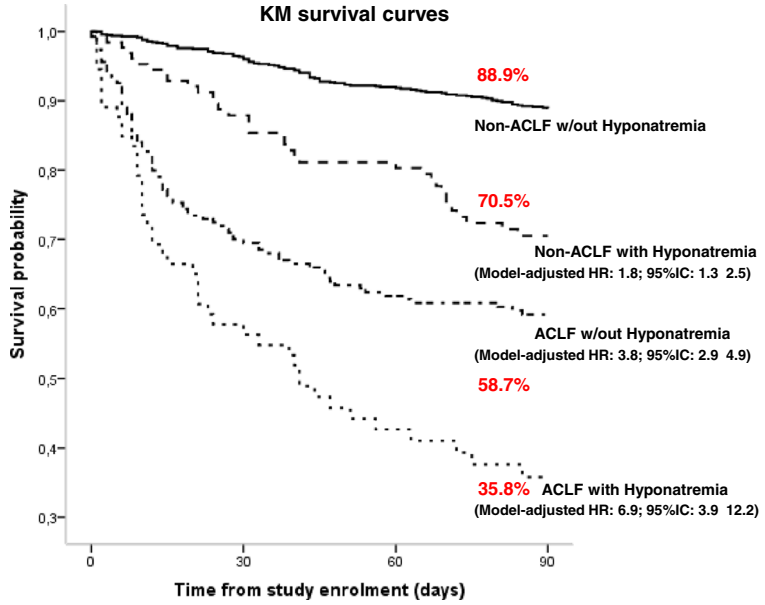


Figure 2 Transplant-free survival curves in patients with and without acute-on-chronic liver failure (ACLF) according to the presence of hyponatremia at inclusion. CLIF: chronic liver failure; CLIF-SOFA: chronic liver failure-sequential organ failure assessment; HR: hazard ratio; MELD: model for end-stage liver disease.

in patients with pre-existing chronic liver disease, which is usually related to a precipitating event and associated with increased mortality at three months due to multisystem organ failure [11-13]. So despite the fact that hyponatremia is a well-recognized complication of patients with advanced cirrhosis, a specific analysis of hyponatremia in patients with ACLF had so far not been reported. The investigation of this relationship is clinically relevant, given the important physiological effects of low serum sodium levels and the well-demonstrated relationship between hyponatremia and survival in the global population of patients with decompensated cirrhosis [4-7,15-19]. In this analysis, we have shown that the presence of hyponatremia in patients with ACLF influences outcome. Interestingly, both variables (hyponatremia and ACLF) independently affect this outcome. Thus the presence of hyponatremia in a patient without ACLF significantly increases the risk of dying at 90 days, but when patients with both (ACLF and hyponatremia) are compared to those without either (ACLF and hyponatremia) then there is an even higher risk of dying at 90 days. These findings, to our knowledge, have not been reported in this subset of patients.

As expected, and in keeping with previous studies, the presence of hyponatremia was associated with increased three-month mortality [15-19]. However, a relevant observation of this study was that the prognosis of patients with ACLF was strongly dependent on the presence or absence of concomitant hyponatremia. In fact, patients with ACLF plus hyponatremia had very low three-month survival expectancy compared to that of patients with ACLF without hyponatremia (35.8% vs. 58.7%, respectively; P <0.001). Similar findings were also observed if patients who developed ACLF during hospitalization were taken into consideration (44.5% vs. 61.5%, respectively; P <0.001). On the other hand, in patients without ACLF, the presence or absence of hyponatremia also influenced prognosis, in such a way that the group of patients without ACLF without hyponatremia had an excellent three-month survival, near 90%, much better than that of patients without ACLF but with hyponatremia.

For many years hyponatremia in patients with cirrhosis has been clearly described as an independent risk factor for mortality [4-7]. The mechanisms that drive this poor prognosis are likely related to its occurrence along with other complications of cirrhosis. In a survey study of 997 cirrhotic patients, Angeli *et al.* demonstrated a prevalence of serum sodium ≤130 mmol/L of 21.6% [20]. This patient subgroup had a significantly higher incidence of hepatic encephalopathy (odds ratio (OR) 3.40; 2.35 to 4.92), hepatorenal syndrome (OR 3.45; 2.04 to 5.82), and spontaneous bacterial peritonitis (OR 2.36; 1.41 to 3.93). It is estimated that patients with cirrhosis and hyponatremia have a 25-50% probability of survival at one year and 23% at five years [4,5]. In contrast to what occurs in cirrhosis in patients with ACLF, hyponatremia portends a 35% probability of survival at three months. The mechanistic reason as to why such as difference exists has not been properly assessed, but it is known that in ACLF increasing organ failures certainly drive prognosis,

whereas in decompensated cirrhosis this does not necessarily occur.

Although not a primary endpoint, we found an interesting and previously unreported association between hyponatremia and leukocyte count in these patients. These findings do not reflect the aim of the study, which was to focus on the outcome of patients with ACLF and hyponatremia. Nonetheless two variables, ACLF and leukocyte count, were associated with the presence of hyponatremia in this large cohort of patients. This relationship between leukocyte count and hyponatremia appeared to be independent from bacterial infections, because among patients without bacterial infections, those with hyponatremia had significantly higher leukocyte count than that of patients without hyponatremia. This relationship is intriguing and may have pathophysiological relevance. Alternatively, it could also be possible that cytokines may interfere directly in kidney water metabolism, causing an impaired water excretion as suggested in other disease states [21,22]. In patients without cirrhosis, development of hyponatremia has been associated with inflammatory diseases such meningitis, pneumonia, tuberculosis, encephalitis, human immunodeficiency virus infection, and malaria [23,24]. However, this needs to be properly studied in patients with cirrhosis and also in those with ACLF.

Conclusions

The results of the current study show that there is an important association between hyponatremia and ACLF. Hyponatremia is not only a prognostic marker in patients with ACLF, but influences the outcome of these patients. Mortality rates are clearly different among patients with ACLF with and without hyponatremia. In patients with ACLF prognosis is clearly dependent on its association with hyponatremia.

Additional file

Additional file 1: Figure S1. Transplant-free survival curves in patients with and without ACLF according to the presence of hyponatremia during hospitalization.

Competing interests

The authors declare that they have no competing interests.

Authors contributions

AC acquired, analyzed and interpreted the results; conceived the study and participated in its design; performed the statistical analysis and drafted and revised the manuscript. ES acquired, analyzed and interpreted the results and revised the manuscript. ER acquired, analyzed and interpreted the results and revised the manuscript. RB acquired, analyzed and interpreted the results and revised the manuscript. IG acquired, analyzed and interpreted the results and revised the manuscript. MP acquired, analyzed and interpreted the results; performed the statistical analysis and drafted and revised the manuscript. FS acquired, analyzed and interpreted the results and revised the manuscript. TMW acquired, analyzed and interpreted the results and revised the manuscript. JMG acquired, analyzed and interpreted the results and revised the manuscript. TG acquired, analyzed and interpreted the results and revised the manuscript. MB acquired, analyzed and interpreted the results and revised the manuscript. VA acquired, analyzed and interpreted the results and revised the manuscript. PG acquired, analyzed and interpreted the results; conceived the study and participated in its design; drafted and revised the manuscript. All authors read and approved the final manuscript.

Funding

Public Research grants from Fondo de Investigacin, Instituto de Salud Carlos III PI12/00330. Ethics bodies that approved the study can be found at: http://www.clifconsortium.com/centres.

Author details

[1]GI Unit, Hospital Clinic, University of Barcelona, Carrer Villarroel, 170, 08036 Barcelona, Spain. [2]Liver Unit, Hospital Clinic, University of Barcelona, Carrer Villarroel, 170, 08036 Barcelona, Spain. [3]Data Management Center - CLIF Consortium, Hospital Clinic, Carrer Villarroel, 170, 08036 Barcelona, Spain. [4]AP-HP Hpital Paul Brousse Centre Hpato-Biliaire, University Paris-Sud, UMR-S 785, 12 avenue Paul Vaillant Couturier, 94800 Villejuif, France. [5]Department of Medicine 1, JW Goethe University Hospital, Frankfurt Theodor-Stern-Kai 7, D-60590 Frankfurt am Main, Germany. [6]Department of Gastroenterology and Hepatology, Hospital Universitario Ramn y Cajal, IRYCIS, Carretera. de Colmenar Viejo, km 9100, 28034 Madrid, Spain. [7]Liver Unit, Department of Gastroenterology and Hepatopancreatology, Erasme University Hospital, Universit Libre de Bruxelles, Route de Lennik 808, 1070 Brussels, Belgium. [8]Department of Medical and Surgical Sciences, University of Bologna, Via Giuseppe Massarenti 9, 40138 Bologna, Italy. [9]University of Barcelona, IDIBAPS, CIBEReHD, IRSIN, Carrer Villarroel, 170, 08036 Barcelona, Catalunya, Spain.

Received: 8 July 2014 Accepted: 27 November 2014
Published online: 13 December 2014

References

1. Gins P, Guevara M: **Hyponatremia in cirrhosis: pathogenesis, clinical significance, and management.** *Hepatology* 2008, **48:**1002 1010.
2. European Association for the Study of the Liver: **EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis.** *J Hepatol* 2010, **53:**397 417.
3. Moore KP, Aithal GP: **Guidelines on the management of ascites in cirrhosis.** *Gut* 2006, **55:**vi1 12.
4. Planas R, Montoliu S, Ballest B, Rivera M, Miquel M, Masnou H, Galeras JA, Gimnez MD, Santos J, Cirera I, Morillas RM, Coll S, Sol R: **Natural history of patients hospitalized for management of cirrhotic ascites.** *Clin Gastroenterol Hepatol* 2006, **4:**1385 1394.
5. Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, Fisher RA, Mihas AA: **Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death.** *Hepatology* 2004, **40:**802 810.
6. Biggins S, Rodriguez HJ, Bachetti P, Bass NM, Roberts JP, Terrault NA: **Serum sodium predicts mortality in patients listed for liver transplantation.** *Hepatology* 2005, **41:**32 39.
7. Londoo MC, Crdenas A, Guevara M, Quint L, de Las HD, Navasa M, Rimola A, Garcia-Valdecasas JC, Arroyo V, Gins P: **MELD score and serum sodium in the prediction of survival of patients with cirrhosis awaiting liver transplantation.** *Gut* 2007, **56:**1283 1290.
8. Londoo MC, Guevara M, Rimola A, Navasa M, Taur P, Mas A, Garca-Valdecasas JC, Arroyo V, Gins P: **Hyponatremia impairs early posttransplantation outcome in patients with cirrhosis undergoing liver transplantation.** *Gastroenterology* 2006, **130:**1135 1143.
9. Dawwas MF, Lewsey JD, Neuberger J, Gimson AE: **The impact of serum sodium concentration on mortality after liver transplantation: a cohort multicenter study.** *Liver Transpl* 2007, **13:**1115 1124.
10. Hackworth WA, Heuman DM, Sanyal AJ, Fisher RA, Sterling RK, Luketic VA, Shiffman ML, Maluf DG, Cotterell AH, Posner MP, Stravitz RT: **Effect of hyponatraemia on outcomes following orthotopic liver transplantation.** *Liver Int* 2009, **29:**1071 1077.
11. Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, Arroyo V, Kamath PS: **Acute-on-chronic liver failure.** *J Hepatol* 2012, **57:**1336 1348.
12. Jalan R, Yurdaydin C, Bajaj JS, Acharya SK, Arroyo V, Lin HC, Gines P, Kim WR, Kamath PS, World Gastroenterology Organization Working Party: **Toward an**

improved definition of acute-on-chronic liver failure. *Gastroenterology* 2014, **147:**4 10.
13. Moreau R, Jalan R, Gines P, Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, Durand F, Gustot T, Saliba F, Domenicali M, Gerbes A, Wendon J, Alessandria C, Laleman W, Zeuzem S, Trebicka J, Bernardi M, Arroyo V, CANONIC Study Investigators of the EASL-CLIF Consortium: **Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis.** *Gastroenterology* 2013, **144:**1426 1437.
14. Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Gins P, Levesque E, Durand F, Angeli P, Caraceni P, Hopf C, Alessandria C, Rodriguez E, Solis-Muoz P, Laleman W, Trebicka J, Zeuzem S, Gustot T, Mookerjee R, Elkrief L, Soriano G, Cordoba J, Morando F, Gerbes A, Agarwal B, Samuel D, Bernardi M, Arroyo V, CANONIC study investigators of the EASL-CLIF Consortium: **Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure.** *J Hepatol* 2014, **61:**1038 1047.
15. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM: **Hyponatremia and mortality among patients on the liver-transplant waiting list.** *N Engl J Med* 2008, **359:**1018 1026.
16. Porcel A, Daz F, Rendn P, Macas M, Martn-Herrera L, Girn-Gonzlez JA: **Dilutional hyponatremia in patients with cirrhosis and ascites.** *Arch Intern Med* 2002, **162:**323 328.
17. Arroyo V, Rods J, Gutirrez-Lizrraga MA, Revert L: **Prognostic value of spontaneous hyponatremia in cirrhosis with ascites.** *Am J Dig Dis* 1976, **21:**249 256.
18. Jalan R, Elton RA, Redhead DN, Finlayson ND, Hayes PC: **Analysis of prognostic variables in the prediction of mortality, shunt failure, variceal rebleeding and encephalopathy following the transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage.** *J Hepatol* 1995, **23:**123 128.
19. Borroni G, Maggi A, Sangiovanni A, Cazzaniga M, Salerno F: **Clinical relevance of hyponatraemia for the hospital outcome of cirrhotic patients.** *Dig Liver Dis* 2000, **32:**605 610.
20. Angeli P, Wong F, Watson H, Gines P: **Hyponatremia in cirrhosis: results of a patient population survey.** *Hepatology* 2006, **44:**1535 1542.
21. Watanabe T, Abe Y, Sato S, Uehara Y, Ikeno K, Abe T: **Hyponatremia in Kawasaki disease.** *Pediatr Nephrol* 2006, **21:**778 781.
22. Eisenhut M: **Changes in renal sodium transport during a systemic inflammatory response.** *Pediatr Nephrol* 2006, **21:**1487 1488.
23. Park SJ, Shin JI: **Inflammation and hyponatremia: an underrecognized condition?** *Korean J Pediatr* 2013, **56:**519 522.
24. Swart RM, Hoorn EJ, Betjes MG, Zietse R: **Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation.** *Nephron Physiol* 2011, **118:**45 51.

doi:10.1186/s13054-014-0700-0
Cite this article as: Crdenas *et al.*: Hyponatremia influences the outcome of patients with acute-on-chronic liver failure: an analysis of the CANONIC study. *Critical Care* 2014 **18**:700.

4. DISCUSSION

Study 1 *- Cárdenas A, Ginès P, Marotta P, Czerwiec F, Oyuang J, Guevara M, Afdhal NH. Tolvaptan, an oral vasopressin antagonist, in the treatment of hyponatremia in cirrhosis. J Hepatol. 2012 Mar;56(3):571-8*.

This study analyzed the specific findings in the subgroup of patients with cirrhosis enrolled in the SALT 1 and 2 studies. The results indicate that use tolvaptan for 1 month effectively increased serum sodium concentration in hyponatremic patients with cirrhosis. Compared to placebo tolvaptan also caused a significant increase in urine output and fluid intake and a negative fluid balance during first day after the initial dose. There also was a significant improvement in some components of health related quality of life (SF 12 health survey mental component scores) at the end of the study. Serum sodium levels reverted to baseline levels 1week after stopping tolvaptan.

This analysis is unique because it specifically evaluates in a population of cirrhotics the safety and efficacy of the only approved oral vaptan for hyponatremia in this population. Tolvaptan significantly increased in the average daily levels of serum sodium concentrations from baseline to the first four days also from baseline to 1 month after the first dose. In fact, tolvaptan was superior to placebo in raising serum sodium levels at all time points from day 1 to day 30 and brought more patients into the normal range more quickly. An important point to take into account is that both the increase in serum sodium levels while on drug and the drop of levels 7 days after stopping tolvaptan indicates that V2 receptor antagonism in patients with cirrhosis is an important target.

The proportion of patients on tolvaptan who normalized serum sodium (>135 mmol/L) at day 4 was 41%, as compared to 11% for placebo. On day 30, these proportions were 33% and 19%, respectively. Although half of patients did not achieve levels greater than 135 mmol/L in the tolvapatan group, the proportions were still significantly higher than placebo. A recent study that evaluated the effect of tolvaptan in patients with cirrhosis showed that urine volume increased along with solute-free water clearance within the first days of tolvaptan and serum sodium increased significantly throughout a period of 2 weeks of tolvaptan (51). However the study did not report on the percent of patients who normalized serum sodium. That said these results are similar and indicate that V2 receptor antagonists are effective in raising serum sodium in patients with cirrhosis and hyponatremia. The difficulty in achieving

normal sodium levels (>135 mmol/L) in the majority of subjects with cirrhosis has also been reported in studies of other vaptans such as conivaptan, lixivaptan, and satavaptan. These numbers indicate that is very likely that the mechanisms of blocking V2 receptors addresses only part of the underlying pathophysiology of hypervolemic hyponatremia in cirrhosis.

An important finding in this study was the relationship effect of tolvaptan in patients with renal failure (defined as serum creatinine > 1.5mg/dL). Surprisingly in this analysis diuretics did not influence the treatment with tolvaptan as the majority of patients were on a moderate dose of diuretics. In addition, in subjects taking tolvaptan the increase in serum sodium during the study in the group of patients with serum creatinine >1.5 mg/dL did not reach statistical significance. Additionally the proportion of patients that developed acute kidney injury was similar in both groups. The administration of tolvaptan in this study was safe, with no apparent differences in the development of significant adverse events when compared to the placebo group. Side effects seen more frequently in those treated with tolvaptan compared to placebo included dry mouth and thirst, all attributable to the intrinsic and desired effect of tolvaptan on free-water clearance. An infrequent yet important adverse event was a higher number of patients with gastrointestinal bleeding in the tolvaptan group (n=6).

An interesting effect seen in this population was the improvement in health-related quality of life as determined by the nearly 5-point increase in the mental component score of the SF-12. This change is considered a moderate but clinically significant change nonetheless other effects of HRLQ were not evaluated in the current study since the primary endpoints were related to changes in serum sodium levels from baseline to day 4 and from baseline to day 30. That said a recent study showed that cognitive function, HRQL and companion burden improved patients with cirrhosis and ascites and hyponatremia after 2 weeks of tolvaptan (51).

A meta-analysis evaluated outcomes in 2,266 patients from 12 randomized trials of tolvaptan, satavaptan and lixivaptan. The primary outcome measure was mortality and secondary outcomes included, but were not limited to complications of cirrhosis and mobilization of ascites (58). While the vaptans increased serum sodium, reduced mean body weight (mean difference of -1.82 kg) and increased time to first large volume paracentesis (RR=0.76;0.60-0.83), there was no mortality benefit (RR=1.06;0.90-1.26). There was a significant increase in

thirst (RR=3.97;1.78-8.83) and excessive urine volume of >5L/day (RR=9.96;1.38-71.68). These adverse effects are important particularly in a patient population that is predisposed to encephalopathy limiting access to water and physical deconditioning limiting mobility.

In summary, tolvaptan is effective in raising serum sodium levels in patients with cirrhosis but there are some limitations with this medication in this population. First, the effects of tolvaptan have only been reported in short term studies and longer studies need to be performed. Second, a large study that evaluated the efficacy and safety of tolvaptan in a population with polycystic kidney disease reported a 23% rate of serious hepatic adverse events, mainly elevated liver enzymes (72). Thus the FDA placed a black box warning on the drug limiting its use for patients with liver disease (73). This certainly has limited its widespread use in different countries where it is approved. Thus, in light of the current data, it is difficult to advocate the use of tolvaptan for all patients with cirrhosis and hyponatremia. Perhaps the best candidate patients to treatment with vaptans are patients with severe hyponatremia (<125 mEq/L) awaiting transplantation (18). Use of vaptans in patients not candidates to transplantation should be individualized in each case.

Study 2 *- Cárdenas A, Solà E, Rodríguez E, Barreto R, Graupera I, Pavesi M, Saliba F, Welzel T, Martinez-Gonzalez J, Gustot T, Bernardi M, Arroyo V, Ginès P; CANONIC study investigators of the EASL-CLIF Consortium. Hyponatremia influences the outcome of patients with acute-on-chronic liver failure: an analysis of the CANONIC study. Crit Care. 2014 Dec 13;18(6):700.[Epub ahead of print]*

This is the first analysis of the influence of hyponatremia in patients with and without ACLF. This relationship is of clinical interest because of the known relevant effects of hyponatremia in the outcome of patients with decompensated cirrhosis. This study showed that hyponatremia was present in 15% of all patients enrolled in the CANONIC study (subjects with and without ACLF). Interestingly, ACLF was more commmon in patients with hyponatremia (36%) compared to those without it (20%). On the other hand, the prevalence of hyponatremia in patients with ACLF was double than that in patients without ACLF (24% vs 12%, respectively). Moreover, hyponatremia developed in a further 22% of patients with ACLF throughout hospitalization. In addition, among all patients without ACLF at inclusion, those with hyponatremia (27.7%) developed ACLF more frequently on follow-up compared to those that did not have hyponatremia (10.2%).

The most important finding of this analysis was the demonstration that hyponatremia influences the outcome of patients with ACLF. Moreover, both hyponatremia and ACLF independently affect this outcome. This means that hyponatremia in patients without ACLF significantly increases the risk of dying. However, even more interesting is the fact that if patients have both ACLF and hyponatremia (compared to those without either) then the risk of dying is almost 7 times higher. These findings indicate that hyponatremia influences the outcome of patients with ACLF

Not surprisingly the presence of hyponatremia was associated with increased 3-month mortality in all groups of patients. However the most relevant finding was that the prognosis of patients with ACLF was strongly dependent on the presence or absence of concomitant hyponatremia at enrolment. Patients with ACLF and hyponatremia had a 35 % 3 month survival expectancy compared to that of patients with ACLF without hyponatremia which was 59%. Similar outcomes occurred in patients that developed ACLF during hospitalization. In patients without ACLF, the presence or absence of hyponatremia also influenced prognosis,

meaning that those without hyponatremia and ACLF had a 90% survival at 3 months, much better than that of patients without ACLF and hyponatremia which was 70%.

In the current analysis a previously unreported association between hyponatremia and leukocyte count in patients with cirrhosis was observed. In fact, the only two variables independently associated with the presence of hyponatremia were ACLF and leukocyte count. Interestingly, the relationship between leukocyte count and hyponatremia was independent from bacterial infections because in patients without bacterial infections those with hyponatremia had higher leukocyte counts than those without hyponatremia. The reason as to why this occurs is unknown, however it could also be possible that elevated of cytokines may interfere directly in renal water metabolism, causing an impaired water excretion as suggested in other disease states (74,75). In patients without cirrhosis, development of hyponatremia has been associated with inflammatory diseases such meningitis, pneumonia, tuberculosis, encephalitis, human immunodeficiency virus infection, and malaria (76,77).

Although nonosmotic AVP secretion is a normal physiological response when caused by low effective arterial blood volume, the underlying mechanisms driving this hypersecretion are not completely clear. In fact a significant proportion of patients with hyponatremia and cirrhosis do not respond to treatment with vaptans, which raises the possibility that other mechanisms may play a role in the development of hyponatremia in cirrhosis. Although not specifically studied in patients with ACLF, in this scenario it is possible that elevated levels of leukocytes along with high levels of inflammatory cytokines such as IL-6, or even TNF alfa which have been described in patients with cirrhosis, could also contribute to hyponatremia by augmenting AVP secretion and the subsequent development of hyponatremia (78,79).

In summary the results of the current study show that there is an important association between hyponatremia and ACLF. Moreover, there is a strong association between hyponatremia and systemic inflammatory response. Hyponatremia is not only a prognostic marker of mortality in patients with cirrhosis; it is also a strong prognostic factor of mortality in patients with ACLF either at hospital admission or during follow up.

5. CONCLUSIONS

The main conclusions of this thesis are:

1. The administration of tolvaptan in addition to standard therapy for 1 month is effective in raising and maintaining serum sodium concentrations in patients with cirrhosis and hyponatremia.
2. Tolvaptan caused a significant increase in free water clearance associated with weight loss without renal impairment and normalization of serum sodium to > 135mEq/L in 41% of patients at day 4 and 33% at day 30.
3. Vaptans significantly improved mental score components of health related quality of life in patients with cirrhosis and hyponatremia.
4. Side effects such as thirst and volume depletion were not significantly higher in patients on tolvaptan compared to those on placebo. However those on tolvaptan had an unexplained slightly higher incidence of gastrointestinal bleeding compared to placebo.
5. These findings indicate that the use of tolvaptan warrants further long-term studies to evaluate its safety and efficacy in selected patients with cirrhosis and hyponatremia.
6. Hyponatremia occurs in 15% of all patients with cirrhosis admitted to hospital for the management of an acute decompensation of the disease.
7. ACLF is more common in patients with hyponatremia than in those without it (36% vs. 20%, respectively). The prevalence of hyponatremia in patients with ACLF was double than that in patients without ACLF (24% vs 12%, respectively).
8. There seems to be a relationship between inflammatory markers (i.e. leukocyte count) and hyponatremia in patients with ACLF. This association is independent from bacterial infections, which is in line with the fact that the ACLF is associated with systemic inflammation.
9. There is an important association between hyponatremia and ACLF as hyponatremia influences the outcome of these patients.
10. Mortality rates among patients with ACLF and hyponatremia were significantly higher compared to those patients without hyponatremia. The prognosis of patients with ACLF is dependent on its association with hyponatremia.

6. REFERENCES

1. Dawson A. Historical notes on ascites. Gastroenterology 1960;39:790-91.
2. Reuben A. Out came copious water. Hepatology 2002;36:261-64.
3. Gines P, Cárdenas A, Sola E, Schrier R. Liver disease and the kidney. In Schrier´s Diseases of the Kidney. Schrier R, Coffmann T, Falk RJ, Molitoris B, Neilson E, Eds. Lippincott Williams & Wilkins; Ninth edition 2013, pgs 1965-1996.
4. Planas R, Montoliu S, Ballesté B, et al. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol 2006;4:1385–94.
5. Nazal L, Cárdenas A. Prognostic markers in patients with ascites and hepatorenal syndrome. Dis Markers. 2011;31:139-46.
6. Martin P, DiMartini A, Feng S, Brown R Jr, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation.Hepatology. 2014 ;59:1144-65
7. Arroyo V, Colmenero J. Ascites and hepatorenal syndrome in cirrhosis:pathophysiological basis of therapy and current management. J Hepatol. 2003;38 Suppl 1:S69-89
8. Iwakiri Y, Shah V, Rockey DC. Vascular pathobiology in chronic liver disease and cirrhosis - current status and future directions. J Hepatol. 2014 ;61:912-24.
9. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology. 1988;8:1151-7.
10. Jiménez W, Martinez-Pardo A, Arroyo V, Bruix J, Rimola A, Gaya J, Rivera F,Rodés J. Temporal relationship between hyperaldosteronism, sodium retention and ascites formation in rats with experimental cirrhosis. Hepatology. 1985;5:245-50
11. Bernardi M. Renal sodium retention in preascitic cirrhosis: expanding knowledge, enduring uncertainties. Hepatology. 2002 ;35:1544-1547
12. Wong F, Liu P, Allidina Y, et al. Pattern of sodium handling and its consequences in patients with preascitic cirrhosis. Gastroenterology 1995;108: 1820-1827
13. Schrier RW. Vasopressin and aquaporin 2 in clinical disorders of water homeostasis. Semin Nephrol. 2008;28:289-96
14. Adrogue HJ, Madias NE. Hyponatremia. N Engl J Med 2000;342:1493-9.

15. Sterns RH. Disorders of plasma sodium--causes, consequences, and correction. N Engl J Med. 2015 Jan 1;372(1):55-65
16. Ginès P, Berl T, Bernardi M, et al. Hyponatremia in cirrhosis: from pathogenesis to treatment. Hepatology 1998; 28:851-864.
17. Ginès P, Guevara M. Hyponatremia in cirrhosis: pathogenesis, clinical significance and management. Hepatology 2008; 48: 1002-10
18. Ginès P, Angeli P, Lenz K, Möller S, Moore K, Moreau R, Larsen M, Bernardi M. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010; 53: 397-417.
19. Gianotti R, Cárdenas A. Hyponatremia in cirrhosis*. Gastroenterol Rep* (Oxf). 2014 Feb;2(1):21-6
20. Pereira G, Guevara M, Fagundes C, Solá E, Rodríguez E, Fernández J, Pavesi M, Arroyo V, Ginès P. Renal failure and hyponatremia in patients with cirrhosis and skin and soft tissue infection. A retrospective study. J Hepatol 2012; 56: 1040-6
21. Ishikawa S, Schrier RW. Pathogenesis of hyponatremia: the role of arginine vasopressin. In: Ascites and Renal Dysfunction in Liver Disease. Ginès P, Arroyo V, Rodes J, Schrier R. Eds 2nd edition Blackwell Publishing, Oxford 2005. pgs 305-314
22. Thibonnier M, Conarty DM, Preston JA, et al. Molecular pharmacology of human vasopressin receptors. Adv Exp Med Biol. 1998;449:251-76.
23. Kwon TH, Hager H, Nejsum LN, et al. Physiology and pathophysiology of renal aquaporins. Semin Nephrol 2001;21:231–238.
24. Nielsen S, Frokiaer J, Marples D, et al. Aquaporins in the kidney: from molecules to medicine. Physiol Rev 2002;82:205–244
25. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med. 2006;355:2099-112.
26. Ginès P, Wong F, Watson H, et al. Effects of satavaptan, a selective vasopressin V2 receptor antagonist, on ascites and serum sodium in cirrhosis with hyponatremia: A randomized trial. Hepatology. 2008;48:204-213.
27. Heuman DM, Abou-Assi SG, Habib A, et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. Hepatology.2004; 40:802-10

28. Cárdenas A, Ginès P, Rodes J. Renal Complications. In: Schiff's Diseases of The Liver. Schiff E, Sorrel M, Maddrey W, Eds. 10th Edition. Lippincott Williams & Wilkins, Philadelphia, 2007 *pgs 498-512.*
29. Angeli P, Wong F, Watson H, Gines P. Hyponatremia in Cirrhosis: Results of a Patient Population Survey. Hepatology 2006;44:1535-42.
30. Ginès P, Uriz J, Calahorra B, Garcia-Tsao G, Kamath PS, Del Arbol LR, Planas R, Bosch J, Arroyo V, Rodés J. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. Gastroenterology. 2002;123:1839-47
31. Janičko M, Veselíny E, Abraldes JG, Jarčuška P. Serum sodium identifies patients with cirrhosis at high risk of hepatorenal syndrome. Z Gastroenterol.2013 ;51):628-34.
32. Møller S, Krag A, Bendtsen F. Kidney injury in cirrhosis: pathophysiological and therapeutic aspects of hepatorenal syndromes. Liver Int. 2014;34:1153-63
33. Biggins S, Rodriguez HJ, Bachetti P, et al. Serum sodium predicts mortality in patients listed for liver transplantation. Hepatology 2005;41:32-9.
34. Londoño MC, Cardenas A, Guevara M, et al. MELD score and serum sodium in the prediction of survival of patients with cirrhosis awaiting liver transplantation. Gut 2007;56:1283-90.
35. Londoño MC, Guevara M, Rimola A, et al. Hyponatremia impairs early posttransplantation outcome in patients with cirrhosis undergoing liver transplantation. Gastroenterology 2006;130:1135-43.
36. Dawwas MF, Lewsey JD, Neuberger J, et al. The impact of serum sodium concentration on mortality after liver transplantation: a cohort multicenter study. Liver Transpl 2007;13:1115-24.
37. Arroyo V, Rodés J, Gutiérrez-Lizárraga MA, Revert L. Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. Am J Dig Dis. 1976;21:249-56
38. Porcel A, Díaz F, Rendón P, Macías M, Martín-Herrera L, Girón-González JA. Dilutional hyponatremia in patients with cirrhosis and ascites. Arch Intern Med.2002;162:323-8
39. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008; 359: 1018-26.

40. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, Benson J, Therneau T, Kremers W, Wiesner R, Kamath P, Klintmalm G. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology 2006; 130: 1652-60.
41. Ruf AE, Kremers WK, Chavez LL, Descalzi VI, Podesta LG, Villamil FG. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. Liver Transpl 2005; 11: 336-43.
42. Guevara M, Baccaro ME, Torre A, et al. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analysis. Am J Gastroenterol. 2009 ;104:1382-9.
43. Guevara M, Baccarro ME, Rios J, et al. Risk factors for hepatic encephalopathy in patients with cirrhosis and refractory ascites: relevance of serum sodium concentration. Liver Int. 2010;30:1137-42
44. Qureshi MO, Khokhar N, Saleem A, Niazi TK. Correlation of hyponatremia with hepatic encephalopathy and severity of liver disease. J Coll Physicians Surg Pak. 2014;24(2):135-7
45. Haussinger D, Schliess F. Pathogenetic mechanisms of hepatic encephalopathy. Gut 2008;57:1156-65.
46. Córdoba J, García-Martinez R, Simón-Talero M. Hyponatremic and hepatic encephalopathies: similarities, differences and coexistence. Metab Brain Dis.2010;25:73-80.
47. Follo A, Llovet JM, Navasa M, Planas R, Forns X, Francitorra A, Rimola A, Gassull MA, Arroyo V, Rodés J . Renal impairment after spontaneous bacterial peritonitis in cirrhosis: course, predictive factors and prognosis. Hepatology 1994;20:1495-1501.
48. Ginès A, Escorsell A, Ginès P, Saló J, Jiménez W, Inglada L, et al. Incidence, predictive factors, and prognosis of hepatorenal syndrome in cirrhosis. Gastroenterology 1993;105:229-236
49. Solà E, Guevara M, Rodriguez E, Barreto R, Pavesi M, Arroyo V, E. Smadja-Lew, H.Watson, Ginès P. Hyponatremia is a major factor of the impaired health-related quality of life in patients with cirrhosis and ascites. J Hepatol .2012;57:1199-206
50. Ahluwalia V, Wade JB, Thacker L, Kraft KA, Sterling RK, Stravitz RT, Fuchs M, Bouneva I, Puri P, Luketic V, Sanyal AJ, Gilles H, Heuman DM, Bajaj JS. Differential impact of hyponatremia and hepatic encephalopathy on health-related quality of life and brain metabolite abnormalities in cirrhosis. J Hepatol. 2013 ;59:467-73.

51. Ahluwalia V, Heuman DM, Feldman G, Wade JB, Thacker LR, Gavis E, Gilles H, Unser A, White MB, Bajaj JS. Correction of hyponatraemia improves cognition, quality of life, and brain oedema in cirrhosis. J Hepatol. 2015 ;62:75-82
52. Yun BC, Kim WR, Benson JT, Biggins SW, Therneau TM, Kremers WK, Rosen CB, Klintmalm GB. Impact of pretransplant hyponatremia on outcome following liver transplantation. Hepatology. 2009;49:1610-5
53. Furst H, Hallows KR, Post J, Chen S, Kotzker W, Goldfarb S, Ziyadeh FN, Neilson EG. The urine/plasma electrolyte ratio: a predictive guide to water restriction. Am J Med Sci. 2000;319:240-4
54. Jalan R, Mookerjee R, Cheshire L, Williams R, et al. Albumin infusion for severe hyponatremia in patients with refractory ascites: A randomized clinical trial. J Hepatol 2007;46:232A.
55. McCormick PA, Mistry P, Kaye G, Burroughs AK, McIntyre N. Intravenous albumin infusion is an effective therapy for hyponatraemia in cirrhotic patients with ascites. Gut 1990; 31: 204-207.
56. Yi S, Jeon H, Yoon SH, Cho JY, Shin SG, Jang IJ, Yu KS. Pharmacokinetics and pharmacodynamics of oral tolvaptan administered in 15- to 60-mg single doses to healthy Korean men. J Cardiovasc Pharmacol. 2012;59:315-22.
57. Rozen-Zvi B, Yahav D, Gheorghiade M, Korzets A, Leibovici L, Gafter U. Vasopressin receptor antagonists for the treatment of hyponatremia: systematic review and meta-analysis. Am J Kidney Dis. 2010 ;56:325-37
58. Dahl E, Gluud LL, Kimer N, Krag A. Meta-analysis: the safety and efficacy of vaptans (tolvaptan, satavaptan and lixivaptan) in cirrhosis with ascites or hyponatraemia. Aliment Pharmacol Ther. 2012;36:619-26
59. O'Leary JG, Davis GL. Conivaptan increases serum sodium in hyponatremic patients with end-stage liver disease. Liver Transpl. 2009 ;15:1325-9
60. 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 2003; 37:182–191.
61. Gerbes AL, Gulberg V, Ginès P et al.VPA Study Group.Therapy of hyponatremia in cirrhosis with a vasopressin receptor antagonist: a randomized double-blind multicenter trial. Gastroenterology 2003; 124:933–939.

62. Wong F, Ginès P, Watson H, et al. Effects of a selective vasopressin V2 receptor antagonist, satavaptan, on ascites recurrence after paracentesis in patients with cirrhosis. J Hepatol. 2010;53:283-90.
63. Wong F, Watson H, Gerbes A, et al. Satavaptan for the management of ascites in cirrhosis. Efficacy and safety across the spectrum of ascites severity. Gut 2012. 2012;61:108-1.
64. Okita K, Sakaida I, Okada M, Kaneko A, Chayama K, Kato M, et al. A multicenter, open-label, dose-ranging study to exploratively evaluate the efficacy, safety, and dose-response of tolvaptan in patients with decompensated liver cirrhosis J Gastroenterol 2010;45:979-87.
65. Sakaida I, Yamashita S, Kobayashi T, Komatsu M, Sakai T, Komorizono Y, Okada M, Okita K; ASCITES 14-Day Administration Study Group. Efficacy and safety of a 14-day administration of tolvaptan in the treatment of patients with ascites in hepatic oedema. J Int Med Res. 2013;41:835-47
66. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST)Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007 ;297(12):1319-31
67. Verbalis JG, Adler S, Schrier RW, Berl T, Zhao Q, Czerwiec FS; SALT Investigators. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. Eur J Endocrinol. 2011;164:725-32
68. Jalan R, Gines P, Olson JC, et al. Acute-on chronic liver failure. J Hepatol 2012; 57:1336–1348
69. Jalan R, Yurdaydin C, Bajaj JS, et al. Toward an improved definition of acute-on-chronic liver failure. Gastroenterology. 2014;147:4-10
70. Moreau R, Jalan R, Gines P, et al. Acute-on-Chronic Liver Failure Is a Distinct Syndrome That Develops in Patients With Acute Decompensation of Cirrhosis. Gastroenterology. 2013;144:1426-37
71. Arroyo V. Moreau R, Jalan R, Gines P, On behalf of the investigators of the EASL-CLIF Consortium CANONIC Study. Acute-on-chronic liver failure: A new syndrome that will re-classify cirrhosis. J Hepatol 2015 In press

72. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS; TEMPO 3:4 Trial Investigators. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012;367:2407-18
73. Samsca (Tolvaptan): Drug Safety Communication - FDA Limits Duration and Usage Due To Possible Liver Injury Leading to Organ Transplant or Death. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm350185.htm (Accessed on January 30,2015)
74. Watanabe T, Abe Y, Sato S, Uehara Y, Ikeno K, Abe T. Hyponatremia in Kawasaki disease. Pediatr Nephrol. 2006;21:778-81.
75. Eisenhut M. Changes in renal sodium transport during a systemic inflammatory response. Pediatr Nephrol. 2006 ;21:1487-8
76. Park SJ, Shin JI. Inflammation and hyponatremia: an underrecognized condition? Korean J Pediatr. 2013;56:519-522.
77. Swart RM, Hoorn EJ, Betjes MG, Zietse R. Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation. Nephron Physiol. 2011;118:45–51
78. Navasa M, Follo A, Filella X, Jiménez W, Francitorra A, Planas R, Rimola A,Arroyo V, Rodés J. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. Hepatology. 1998;27:1227-32
79. Francés R, Zapater P, González-Navajas JM, Muñoz C, Caño R, Moreu R, Pascual S, Bellot P, Pérez-Mateo M, Such J. Bacterial DNA in patients with cirrhosis and noninfected ascites mimics the soluble immune response established in patients with spontaneous bacterial peritonitis. Hepatology. 2008;47:978-85.

7. RESUMEN (CASTELLANO)

Valor pronóstico y tratamiento de la hiponatremia en pacientes con cirrosis descompensada y insuficiencia hepática aguda sobre crónica.

RESUMEN – CASTELLANO

1. Introducción y objetivos

La cirrosis es una enfermedad crónica y progresiva que se caracteriza por complicaciones asociadas a la hipertensión portal e insuficiencia hepática. Una complicación común de los pacientes con cirrosis son los trastornos de la función renal que están asociados a una alta morbilidad y un mal pronóstico. Las alteraciones en la función renal de estos pacientes incluyen la retención de sodio y agua libre y la vasoconstricción renal. La retención de sodio es responsable de la formación de ascitis y edemas, mientras que la retención de agua libre de solutos origina una hiponatremia hipervolemica, y la vasoconstricción renal da lugar al desarrollo del síndrome hepatorrenal. Debido a su mal pronóstico la presencia de estas complicaciones son indicaciones de trasplante hepático. Dentro de estas complicaciones la hiponatremia hipervolemica destaca debido a que juega un papel muy importante en el pronóstico de estos pacientes. Varios estudios han permitido identificar factores pronósticos en estos pacientes y aplicar nuevos tratamientos para la hiponatremia. La hiponatremia hipervolémica se define como una concentración sérica de sodio ≤ 130 mEq/L en pacientes con cirrosis y ascitis que no estén deshidratados. Este trastorno debe distinguirse de la hiponatremia hipovolémica que puede ocurrir en aquellos pacientes que presentan una respuesta muy marcada a los diuréticos que comporta deshidratación e insuficiencia renal. La hormona antidiurética o arginina vasopresina (AVP) es el principal factor que determina la reabsorción de agua libre en el segmento distal de la nefrona. La patogenia de la retención de agua libre en la cirrosis es compleja e involucra diferentes factores, siendo el principal la secreción no osmótica de AVP. Los elevados niveles plasmáticos de AVP son consecuencia de la hipersecreción no osmótica de esta hormona que ocurre debido a la vasodilatación esplácnica existente en la cirrosis que estimula la producción de sustancias vasoactivas tales como la renina, norepinefrina y AVP.

La información disponible acerca del curso y las consecuencias clínicas de la hiponatremia dilucional en la cirrosis es limitada. Algunos enfermos no presentan síntomas mientras que otros pueden tener encefalopatía hepática asociada lo cual hace difícil la identificación de

síntomas específicos. La hiponatremia en pacientes con cirrosis se desarrolla en general de forma lenta y suele ser moderada. La mayoría de pacientes con hiponatremia tienen niveles de sodio sérico que oscilan entre 125 y 130 mEq/L. Los niveles bajos de sodio sérico son marcadores de mal pronóstico en pacientes con cirrosis y en espera del trasplante hepático. La hiponatremia predice la mortalidad en los pacientes con cirrosis y ascitis en lista para trasplante hepático y el valor predictivo del sodio sérico en algunos estudios ha demostrado ser independiente del Model for End-Stage Liver Disease (MELD) por lo tanto la adición del sodio sérico al modelo MELD (formula MELD-Na) parece mejorar el valor predictivo del MELD para la mortalidad en lista de espera para trasplante hepático

El tratamiento convencional de la hiponatremia hipervolémica es la restricción de líquidos a 1,5 litros al día. Sin embargo, esta medida es difícil de realizar y raramente es eficaz. La administración de sodio en forma de solución salina endovenosa está contraindicada porque lleva inevitablemente a la acumulación de más ascitis y edema. Nuevos fármacos que antagonizan de forma selectiva el receptor V2 de la AVP en los túbulos renales y, por lo tanto, inhiben la reabsorción de agua libre han sido estudiados en pacientes con hiponatremia hipervolemica. Estos agentes aumentan la excreción renal de agua libre de solutos y son útiles para mejorar la hiponatremia en los pacientes con enfermedades asociadas con retención de agua libre tales como insuficiencia cardíaca congestiva o el síndrome de secreción inapropiada de AVP. Aunque hay varios estudios de estos antagonistas del receptor V2 en modelos animales de cirrosis, los datos en pacientes con cirrosis son todavía escasos. Los medicamentos estudiados son el satavaptan, lixivaptan y tolvaptan. De estos tres solo el tolvaptan está aprobado en Europa y Estados Unidos para el tratamiento de la hiponatremia hipervolemica. Dado que no existen datos acerca del uso del tolvaptan exclusivamente en pacientes con cirrosis, el objetivo del primer estudio de esta tesis se centra en el papel del tolvaptan en pacientes con cirrosis, ascitis e hiponatremia.

La insuficiencia hepática aguda sobre crónica (IHAC) se considera un deterioro agudo de la función hepática en pacientes con hepatopatía crónica previa, generalmente secundario a un factor precipitante (intra o extrahepático) y con un elevado riesgo de mortalidad. La Organización Mundial de Gastroenterología lo define como síndrome en pacientes con enfermedad hepática crónica con o sin cirrosis previamente diagnosticada que se caracteriza por una descompensación hepática aguda que resulta en insuficiencia hepática (ictericia y prolongación del tiempo de protrombina) y uno o más fallos orgánicos extrahepáticos que se

asocia con una mayor mortalidad en un período de 28 días y hasta 3 meses desde el inicio. La definición se basa principalmente en un estudio prospectivo, multicéntrico, observacional realizado por el Consorcio CLIF en 8 centros europeos (Estudio CANONIC). En el estudio, los autores fueron capaces de diferenciar los pacientes con IHAC de los no-IHAC (es decir, los pacientes con un simple descompensación) según criterios predefinidos que fueron validados prospectivamente. La descompensación aguda fue definida por el desarrollo de la hemorragia gastrointestinal, infecciones bacterianas, ascitis o cualquier combinación de estos eventos. Los investigadores entonces utilizaron una puntuación SOFA modificada (escala CLIF-SOFA) para definir el fracaso (s) de órganos. Esta escala fue diseñada antes del inicio del estudio y se evaluó la función de 6 sistemas (hígado, riñones, el cerebro, la coagulación, la circulación y los pulmones). La insuficiencia renal aguda se asoció con mayor mortalidad en comparación con cualquier otra falla orgánica única. En el estudio, la prevalencia global de IHAC fue del 30,9%, con una tasa de mortalidad a los 90 días del 49%. Entre las variables analizadas como factores de riesgo en relación con los sistemas antes mencionados, solo la ascitis, y un alto recuento de leucocitos fueron factores predictivos para el desarrollo de la mortalidad en pacientes con IHAC, pero otros factores como la hiponatremia no surgieron como factor predictivo de mortalidad en estos pacientes.

Como se describió anteriormente la presencia de hiponatremia se asocia con un mal pronóstico en pacientes con cirrosis avanzada. Sin embargo, durante la historia natural de los pacientes con cirrosis pueden desarrollar descompensaciones agudas que pueden manifestarse por una o más complicaciones tales como la aparición de ascitis, encefalopatía hepática, hemorragia gastrointestinal, y / o infecciones bacterianas. Estos eventos agudos pueden ocurrir espontáneamente, pero más comúnmente aparecen en relación con distintos fallos orgánicos (es decir, hígado, riñón, cerebro, circulatorios y pulmonares o fallas de coagulación). La reciente definición de IHAC se basa en el tipo y grado de fallos orgánicos que ayudan a estratificar y determinar el pronóstico para pacientes con y sin IHAC. Dado que la hiponatremia es un potente marcador pronóstico en pacientes con cirrosis sin IHAC, el objetivo del segundo estudio de esta tesis es describir el impacto de la hiponatremia en pacientes con IHAC.

2. Resultados- Ver publicaciones adjuntas

1. **Cardenas A**, Gines P, Marotta P, Czerwiec G, Oyuang J, Guevara M, Afdhal N . The safety and efficacy of tolvaptan, an oral vasopressin antagonist in the treatment of hyponatremia in cirrhosis. *J Hepatol* 2012 Mar;56(3):571-8

2. **Cárdenas A**, Solà E, Rodríguez E, Barreto R, Graupera I, Pavesi M, Saliba F, Welzel T, Martinez-Gonzalez J, Gustot T, Bernardi M, Arroyo V, Ginès P; CANONIC study investigators of the EASL-CLIF Consortium. Hyponatremia influences the outcome of patients with acute-on-chronic liver failure: an analysis of the CANONIC study. Crit Care. 2014 Dec 13;18(6):700

3. Discusión

Estudio 1-

Este estudio analizó los hallazgos específicos en un subgrupo de pacientes incluidos en los estudios SALT 1 y 2. Los resultados indican que el tolvaptan administrado durante 30 días aumentó de una manera eficaz la concentración sérica de sodio en los pacientes con cirrosis e hiponatremia. También se observó una mejora significativa en algunos componentes de la calidad de vida (encuesta de salud SF12, en las puntuaciones de los componentes mentales) al final del estudio. Los niveles de sodio sérico volvieron a los niveles basales 1 semana después de suspender tolvaptan. Este análisis es único, ya que evalúa específicamente en una población de pacientes con cirrosis, la seguridad y eficacia de único vaptan oral aprobado para la hiponatremia. El tolvaptan aumentó significativamente los niveles promedios diarios de las concentraciones séricas de sodio al ser administrado durante un mes. De hecho, tolvaptan fue superior al placebo en el aumento de los niveles de sodio sérico desde del día 1 hasta el día 30. La proporción de pacientes tratados con tolvaptan que normalizaron sodio sérico (> 135 mmol / l) en 4 días fue del 41%, en comparación con 11% para el placebo. A los 30 dias, estas proporciones fueron 33% y 19%, respectivamente. El uso del tolvaptan fue seguro y sin diferencias aparentes en el desarrollo de eventos adversos significativos en comparación con el grupo placebo. Los efectos secundarios observados con mayor frecuencia en los pacientes tratados con tolvaptan en comparación con el placebo incluyeron boca seca y sed, todo atribuible al efecto intrínseco y deseado de tolvaptan en el aclaramiento de agua libre. Un

evento adverso poco frecuente pero importante era un mayor número de pacientes con sangrado gastrointestinal en el grupo de tolvaptan (n = 6).

Estudio 2-

Este es un análisis que examina la influencia de la hiponatremia en pacientes con y sin IHAC. Esta relación es de interés clínico debido al efecto conocido de la hiponatremia en la evolución de los pacientes con cirrosis descompensada. Este estudio mostró que la hiponatremia estaba presente en el 15% de todos los pacientes incluidos en el estudio CANONIC (sujetos con y sin IHAC). La IHAC estaba presente en el 36% de pacientes con hiponatremia en comparación al 20% de aquellos sin hiponatremia. Por otra parte, la prevalencia de la hiponatremia en pacientes con IHAC fue el doble comparado a los pacientes sin IHAC (24% vs 12%, respectivamente). El hallazgo más importante de este análisis fue la demostración de que la hiponatremia influye en el desenlace de los pacientes con IHAC. Tanto la hiponatremia y IHAC afectan de forma independiente este resultado. Esto significa que la hiponatremia en pacientes sin IHAC aumenta significativamente el riesgo de mortalidad. Sin embargo, aún más interesante es el hecho de que si los pacientes tienen tanto IHAC e hiponatremia (en comparación con los que no tienen ninguno de los dos), entonces el riesgo de mortalidad es casi 7 veces mayor. Estos hallazgos indican que la hiponatremia influye de manera significativa en el desenlace de los pacientes con IHAC

No es de extrañar que la presencia de hiponatremia se asociara a una mayor mortalidad a 3 meses en todos los grupos de pacientes. Pero el hallazgo más relevante fue que el pronóstico de los pacientes con IHAC dependía en gran medida de la presencia o ausencia de la hiponatremia concomitante de los pacientes al ser incluidos en el estudio. Los pacientes con hiponatremia IHAC y tenían una supervivencia de 35% a los 3 meses en comparación con la de los pacientes con hiponatremia sin IHAC que era del 59%. Se observaron resultados similares en aquellos pacientes que desarrollaron IHAC durante la hospitalización. En pacientes sin IHAC, la presencia o ausencia de la hiponatremia también influyó en el pronóstico, lo que significa que aquellos sin hiponatremia y IHAC tenían una supervivencia del 90% a los 3 meses, la cual era mucho mejor que la de los pacientes sin IHAC e hiponatremia la cual era del 70%.

4. Conclusiones

- La administración de tolvaptan durante 1 mes es eficaz y aumenta las concentraciones de sodio sérico en pacientes con cirrosis e hiponatremia.
- El tolvaptan causó un aumento significativo en el sodio sérico con la normalización de sodio sérico a> 135mEq / L en 41% de los pacientes en el día 4 y el 33% en 30 días.
- El medicamento mejoró significativamente los componentes de puntuación mental de de calidad de vida en los pacientes con cirrosis e hiponatremia.
- Los efectos secundarios no fueron significativamente mayores en los pacientes tratados con tolvaptan en comparación a los tratados con placebo.
- Estos resultados indican que el uso de tolvaptan merece más estudios a largo plazo para evaluar su seguridad y eficacia en pacientes con cirrosis e hiponatremia.
- La hiponatremia ocurre en el 15% de todos los pacientes con cirrosis ingresados en el hospital para el tratamiento de una descompensación aguda de la cirrosis.
- IHAC es más común en pacientes con hiponatremia que en aquellos sin ella (36% vs. 20%, respectivamente). La prevalencia de la hiponatremia en pacientes con IHAC era el doble que en los pacientes sin IHAC (24% vs 12%, respectivamente).
- Parece que hay una relación entre los marcadores inflamatorios (es decir, recuento de leucocitos) y la hiponatremia en pacientes con IHAC. Esta asociación es independiente de infecciones bacterianas, que concuerda con el hecho de que el IHAC se asocia con inflamación sistémica.
- Existe una relación importante entre la hiponatremia e IHAC que influye en la evolución de estos pacientes.
- Las tasas de mortalidad entre los pacientes con IHAC e hiponatremia fueron significativamente mayores en comparación con los pacientes sin hiponatremia. El pronóstico de los pacientes con IHAC depende de su asociación con hiponatremia.