treatment. In the end, almost 80% of patients without remission did receive immunosuppressive therapy, largely as a result of worsening renal function or complications of nephrotic syndrome. Taken together with recent findings from a controlled clinical trial of early versus late initiation of immunosuppressive therapy in membranous nephropathy,8 it seems that it is not necessary to initiate specific treatment upon confirmation of the diagnosis by renal biopsy, unless severe symptoms of nephrotic syndrome are present or renal function is on the decline. The seeming lack of benefit from ACEI or ARB therapy in patients with baseline proteinuria of 2-8 g/d is remarkable,5 but this needs confirmation in a randomized, controlled trial. At present, although ACEIs and ARBs are often recommended as part of the nonimmunosuppressive management of membranous nephropathy,9 this is not evidence-based guidance.

Not surprising, the long-term outcome of those with complete or partial spontaneous remissions is excellent: Mortality rate was 2%, and ESRD risk was 0%.5 Conversely, the risks of persistent nephrotic syndrome in membranous nephropathy are considerable: Mortality rate was 11%, and ESRD risk was 19%. Relapses after a spontaneous remission seem quite infrequent (5.7%) and easy to manage.5 For unclear reasons, this relapse rate after a spontaneous remission is substantially lower than when a remission is therapeutically induced with immunosuppressive drugs.10

The GLOSEN study6 offers much in the way of reassurance and guidance to the treating physician but does not shed much light on the mechanisms underlying the behavior of membranous nephropathy as a self-limiting disease in many patients. More questions naturally arise as we enter a new era of understanding the pathogenesis of membranous nephropathy as a podocytopathy induced by circulating autoantibodies to well-defined antigens intrinsic to visceral epithelial cells along the glomerulus.11-13

What triggers the appearance of these autoantibodies, and are spontaneous remissions associated with their disappearance? If these autoantibodies disappear with spontaneous remission, then spontaneous remissions associated with their disappearance? If these autoantibodies disappear with spontaneous remission, then which immune events are responsible for this self-regulating phenomenon? Do spontaneous remissions differ mechanistically from therapeutically induced remissions? Are differing agents similar or discordant in their underlying mechanisms for induction of remissions? The answers to these and more questions are likely to be forthcoming in the not-too-distant future. Until then, the study of Polanco et al.5 will stand as an important reference for examining the course of membranous nephropathy unmodified by immunosuppressive drugs, with valuable caveats for managing this all-too-common disorder.

DISCLOSURES
None.

REFERENCES


Treatment of Chronic Hyponatremia: Now We Know How, but Do We Know When or If?

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Two vasopressin receptor antagonists (vaptans) are now available for treatment of euvoletic or hypervolemic hyponatremia in the United States. The Food and Drug Administration approved conivaptan, a combined V1a/V2 receptor antagonist, in December 2005. Although orally active, marketing was limited to a parenteral form intended for short-term hospital use because of concern for the drug’s potency as a CYP3A4 inhibitor. Tolvaptan, a selective V2 receptor antagonist, was approved in May 2009. Like conivaptan, it has been shown in short-term studies to be effective in raising the serum sodium concentration in patients with diverse causes of hyponatremia. Until now, almost all of the published experience with vaptans in hyponatremia has come from studies of short duration, ranging from a single dose to 30 days of therapy. Longer term experience with conivaptan is convincing but anecdotal; even a single study that used satavaptan to treat hyponatremia for up to 12 months had only 10 patients.

In this issue of JASN, important data on the long-term use of vaptan therapy in a much larger cohort are presented by Berl et al. Termed Safety and sodium Assessment of Long-term Tolvaptan With hyponatremia: A year-long, open-label Trial to gain Experience under Real-world conditions (SALTWATER), it was an open-label extension of the earlier Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT) in which SALT enrollees who previously received either tolvaptan or placebo for 30 days were given oral tolvaptan for up to 804 days. A total of 111 individuals participated in SALTWATER, and, over time, 64 discontinued the drug, 30 because of death or adverse reactions. The median time on the drug was 639 days. At 50 weeks, the serum sodium concentration had normalized in approximately 60% of patients. With additional passage of time, the fraction of patients with nornonatremia rose, but the patient dropout rate was substantial. Compared with patients with the syndrome of inappropriate antidiuretic hormone secretion or congestive heart failure as the cause of hyponatremia, fewer patients with cirrhosis achieved nornonatremia. This is an interesting and provocative finding, but only four patients with cirrhosis were followed for as long as 106 weeks. Specific reasons for patient dropout are not given, so it is uncertain what accounts for the high attrition rate among patients with cirrhosis. Similarly, because neither urine osmolality nor renal function data were provided, it is not possible to draw conclusions about a mechanism for reduced efficacy in patients with cirrhosis.

The vaptans work just as other agents that interfere with vasopressin: By binding to the V2 vasopressin receptor on renal collecting duct cells. After vaptan administration, urine osmolality falls, an aquaresis—an electrolyte-free diuresis with increased free water clearance—occurs and the serum sodium concentration rises. It is not surprising, therefore, that the most common adverse effects potentially related to the drug were frequent daytime urination (pollakiuria), thirst, dry mouth, polydipsia, and polyuria; however, nine possible and one probable drug-related serious adverse events were reported as well. One of these adverse events, the development of hepatorenal syndrome in a 65-year-old woman whose hyponatremia was due to cirrhosis, led to the patient’s death and was deemed possibly related to tolvaptan. Even so, this moderate number of adverse events during a total drug exposure of 77,369 patient-days, many in patients with advanced congestive heart failure or cirrhosis, constitutes an acceptable safety profile for long-term use. In SALTWATER, as in all other trials of vaptans to date, the rate of rise of serum sodium concentration was easily controlled, and no patient developed osmotic demyelination. More than 2000 patients with heart failure also received tolvaptan with a median follow-up of 9.9 months in the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) trial without significant ill effect, providing some additional assurance that the drug is free of significant idiosyncratic effects.

SALTWATER suffers from the obvious limitations of any open-label study and the additional difficulties that accrue owing to the poor prognosis of hyponatremia with heart failure and cirrhosis. Nonetheless, the trial shows the majority of patients benefit from the drug with a reduced need for fluid restriction and improved serum sodium concentration. The alternative treatments for chronic hyponatremia include urea, lithium, and demeclocycline, drugs that all are not approved as treatments for hyponatremia and unpalatable or potentially unsafe.

Vaptans are an elegant and attractive approach to treatment of vasopressin-induced hyponatremia, but elegance is not enough. Conivaptan has been available in the United States for nearly 5 years, but it is seldom used, even though hyponatremia is the most common electrolyte disorder in hospitalized patients. In part, this is because the drug must be given intravenously, but the real impediment to starting conivaptan is that it cannot be used long term. What is one to do after the 4-day infusion is over?

The approval of tolvaptan moves us one step further, because this drug is available in oral form, which is suitable for long-term administration. Now SALTWATER has established that tolvaptan successfully corrects chronic hyponatremia in a large proportion of patients who are treated long term. None of the placebo-controlled vaptan studies included patients with severe neurologic symptoms such as seizures, and hypertonic saline remains the recommended treatment for such patients; however, in light of SALTWATER, tolvaptan will become the drug of choice for treatment of symptomatic chronic hyponatremia except in the setting of urgency.

Unfortunately, this is not the whole story. The success of SALTWATER brings the key unanswered question about hyponatremia into sharp relief: Should we treat chronic hy-
ponatremia in patients who lack obvious symptoms? We know that hyponatremia in the syndrome of inappropriate antidiuretic hormone secretion, heart failure, and cirrhosis is mediated by vasopressin.\textsuperscript{13–15} We also know that hyponatremia associates with increased mortality in heart failure and cirrhosis.\textsuperscript{8–10} What we do not know is whether the hyponatremia in these seriously ill patients is itself harmful or merely a marker of worsening disease. Even mild hyponatremia associates with increased medical costs,\textsuperscript{16} and mortality in both the general hospitalized population and in community-dwelling elderly individuals suggests hyponatremia is not an epiphenomenon.\textsuperscript{17,18} Apart from trying to determine whether treating asymptomatic hyponatremia would reduce cost or mortality, however, it is important to ask also whether such treatment would reduce morbidity.

Several lines of emerging evidence suggest it would. Hyponatremia predisposes to falls, and correction of hyponatremia reduces gait impairment and improves alertness.\textsuperscript{19} In ponatremic patients with congestive heart failure.\textsuperscript{20} Several lines of emerging evidence suggest it would. Hyponatremia is not an epiphenomenon.\textsuperscript{17,18} Apart from trying to determine whether treating asymptomatic hyponatremia would reduce cost or mortality, however, it is important to ask also whether such treatment would reduce morbidity.

In this age of evidence-based medicine, clinicians expect every new treatment to be backed by studies with hard end points. Although SALTWATER shows that we can treat chronic hyponatremia successfully with tolvaptan, its metric was serum sodium and was not designed or powered to assess improvement in symptoms or survival. For now, clinicians must rely on good judgment rather than unequivocal evidence to decide which patients with chronic hyponatremia should be given tolvaptan. The availability of an effective treatment for chronic hyponatremia makes the need for data to inform that decision even more acute.

REFERENCES


