Cost-effectiveness of Tolvaptan for Euvolemic or Hypervolemic Hyponatremia

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ABSTRACT

Purpose: Tolvaptan is clinically effective in increasing serum sodium concentrations for patients with euvolemic or hypervolemic hyponatremia. Appropriate treatment of hyponatremia may reduce the risk of death, hospital resource utilization, and economic burden. The aim of this study was to estimate the cost-effectiveness of tolvaptan treatment in patients who need to be hospitalized for treatment and monitoring of euvolemic or hypervolemic hyponatremia.

Methods: A decision-analytic model was constructed to assess the clinical and economic impact of tolvaptan compared with placebo during a 1-month treatment period. The probabilities, utility weights, resource utilization, and costs in the model were derived from clinical trials, survey research, and the Korean National Health Insurance database. Cost analysis was performed from the perspective of the South Korean health care setting in 2012 Korean won (KRW). The model outcome was the incremental cost per quality-adjusted life-year gained. In addition, subgroup analysis was performed to identify the cost-effectiveness in case of tolvaptan treatment only for patients with marked hyponatremia. Deterministic and probabilistic sensitivity analyses were performed on key model parameters and assumptions.

Findings: The total cost per patient was KRW 1,826,771 for tolvaptan treatment and KRW 2,281,926 for placebo. The quality-adjusted life-years for treatment with and without tolvaptan were 0.0481 and 0.0446, respectively. The base-case analysis revealed that tolvaptan was a more effective and less expensive strategy compared with placebo. In the subgroup analysis, this trend was more apparent in case of tolvaptan treatment only for patients with marked hyponatremia. The robustness of the results was confirmed by using deterministic and probabilistic sensitivity analyses.

Implications: This cost-effectiveness analysis found that the use of tolvaptan was less expensive and more effective than treatment without tolvaptan in patients with euvolemic or hypervolemic hyponatremia. (*Clin Ther*. 2014;36:1183–1194)

Key words: cost-effectiveness, decision-analytic model, hyponatremia, tolvaptan.

INTRODUCTION

Hyponatremia is a common electrolyte disorder occurring in clinical practice, especially in hospitalized patients.[1,2] It is often defined as a decrease in the serum sodium level to <136 mmol/L.[3] Hyponatremia during hospitalization is associated with a number of conditions and diseases, including infections, surgery, medication use, syndrome of inappropriate antidiuretic hormone secretion (SIADH), congestive heart failure, cirrhosis with ascites, and any other clinically acute condition.[4] The estimated daily incidence and prevalence of hyponatremia were 0.97% and 2.48%, respectively, in hospitalized patients; two thirds of all hyponatremia episodes occur during the course of hospitalization.[5] A higher frequency of hyponatremia was observed in 14% to 30% of hospitalized patients in the intensive care unit.[2,6]

Hyponatremia is associated with substantial morbidity and mortality, and its severity depends on the rapidity

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of onset and the extent of the decrease in serum sodium concentration.[2,7,8] Most cases of hyponatremia are mild and relatively asymptomatic, but neurologic symptoms may occur if the serum sodium concentration falls suddenly or to a very low level.[9] Moreover, patients with hyponatremia have higher mortality and increased need for intensive care unit and mechanical ventilatory support, as well as longer hospital stays and higher costs, compared with patients without hyponatremia.[6,10–12] Therefore, the resolution of hyponatremia with appropriate treatment may reduce the risk of death, hospital resource utilization, and economic burden.

Tolvaptan is an orally active, selective, nonpeptide vasopressin antagonist that blocks the binding of arginine vasopressin at the V_2-receptors in the distal portions of the nephron, resulting in excretion of electrolyte-free water without depletion of electrolytes.[13–15] Conventional treatments for euvolemic or hypervolemic hyponatremia are water restriction, hypertonic saline, demeclocycline, and urea.[16] However, these treatments have significant disadvantages, including noncompliance, difficulty in controlling the rate of correction, inconsistent efficacy, and adverse events.[17] Tolvaptan was effective in increasing serum sodium concentrations for patients with euvolemic or hypervolemic hyponatremia without clinically significant adverse events.[14]

Despite the clinical efficacy of tolvaptan in the treatment of hyponatremia, there is an economic uncertainty with regard to its use.[13,14,24,25] Tolvaptan is a relatively expensive treatment compared with other currently available treatments for hyponatremia, but the resolution of hyponatremia by tolvaptan may be associated with reduced hospital costs. Therefore, a cost-effectiveness study is necessary to evaluate not only the effectiveness, but also the economic impact, of tolvaptan. To the best of our knowledge, no cost-effectiveness studies of treatment in patients with hyponatremia have yet been conducted. The present analysis was conducted to determine whether tolvaptan is cost-effective compared with placebo in euvolemic or hypervolemic hyponatremia by using a decision-analytic model.

MATERIALS AND METHODS

Study Design

Based on data obtained from randomized controlled trials, a decision-analytic model was constructed to estimate the cost-effectiveness of tolvaptan in patients who need to be hospitalized for treatment and monitoring of hyponatremia.[14] This model was developed to estimate quality-adjusted life-years (QALYs) and costs during a 1-month treatment period. The model outcome was the incremental cost-effectiveness ratio (ICER), which is defined as the ratio of the change in costs to the incremental effectiveness of tolvaptan compared with placebo. Cost analysis was performed from the perspective of the South Korean health care setting in 2012 Korean won (KRW); the discount rate was not applied to either costs or effectiveness. All analyses were conducted by using TreeAge Pro 2012 (TreeAge Software, Inc, Williamstown, Massachusetts; www.treeage.com).

Population

The modeled population included those studied in the tolvaptan clinical trials[14]: patients with euvolemic or hypervolemic hyponatremia, defined as a nonartifactual serum sodium level <135 mEq/L. At the start of the model, study subjects included inpatients for chronic heart failure, liver cirrhosis, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in association with hyponatremia. These patients required hospitalization for treatment of hyponatremia or their primary disease and monitoring of serum sodium concentration during treatment. The proportion of patients who had mild hyponatremia (serum sodium, 130–135 mEq/L) were almost similar to that who had marked hyponatremia (serum sodium, <130 mEq/L). Patients did not require treatment with mandated fluid restriction or a change in medication regimen, such as the use of diuretics, for their primary disease.

Model Structure

Figure 1 displays the structure of the model, which followed the natural course of hyponatremia treatment. This model compared the use of tolvaptan with placebo (no medication for hyponatremia), with nonmandatory fluid restriction in both treatment groups in case of need. Fluid restriction is generally the treatment of choice for euvolemic or hypervolemic hyponatremia, but it is not the optimal therapy in all cases because it is ineffective or intolerable for some patients with hyponatremia.[3,18] Therefore, placebo with nonmandated fluid restriction was used as a comparator.

After initial treatment with tolvaptan or placebo, the change in hyponatremia status was classified into 3 categories (normonatremia [>135 mEq/L], mild hyponatremia [130–135 mEq/L], and marked hyponatremia