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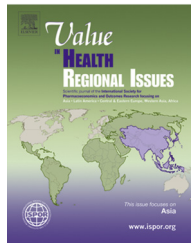

Cost-Utility Analysis of Erythropoietin for Anemia Treatment in Thai End-Stage Renal Disease Patients with Hemodialysis

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ABSTRACT

Objective: To compare the cost utility of using erythropoietin (EPO) to maintain different hemoglobin (Hb) target levels in hemodialysis patients from a societal perspective. **Methods:** A Markov model was used to estimate the incremental cost and quality-adjusted life-year of five Hb levels: 9 or less, more than 9 to 10, more than 10 to 11, more than 11 to 12, and more than 12 g/dl. A systematic review of EPO treatment in hemodialysis patients was conducted to estimate transitional probabilities. Cost data were estimated on the basis of the reference price of Siriraj Hospital, the largest university hospital in Thailand. Utility scores were derived from the six-dimensional health state short form (derived from short-form 36 health survey), which were collected from 152 hemodialysis patients receiving EPO at Siriraj hospital. Probabilistic sensitivity analysis was conducted to investigate the effect of uncertain parameters. All future costs and outcomes were discounted at the rate of 3% per annum. **Results:** The incremental cost-effectiveness ratios of Hb levels more than 9 to 10, more than 10 to 11, more than 11 to 12, and more than 12 g/dl compared with the least costly option (Hb $\leq$ 9 g/dl) were US $24,128.03, US $18,789.07, US $22,427.36, and US $28,022.33 per quality-adjusted life-year, respectively. From probabilistic sensitivity analysis, the hemoglobin level of more than 10 to 11 g/dl was appropriate when the willingness to pay was US $15,523.88 to US $46,610.17 and the probability of cost-effective was 29.32% to 95.94%. **Conclusions:** Providing EPO for a hemoglobin level of more than 10 to 11 g/dl had a cost-effectiveness higher than that of doing so for other hemoglobin levels. This finding will be put forward to the policy level to set up the EPO treatment guideline of the hospital for hemodialysis patients.

Keywords: cost-utility analysis, end-stage renal disease, erythropoietin, hemodialysis, Markov model.

Introduction

Twenty-five years have passed since the first patient received recombinant human erythropoietin (EPO) in Seattle in November 1985 [1,2]. EPO is effective in reversing anemia of renal failure and all its diverse consequences. A reduction in hemoglobin (Hb) levels in these patients has been shown to be associated with impairment in quality of life (QOL), reduced energy, neurocognitive decline, decreased exercise capacity, and increased mortality [3–6]. The cause of anemia in the patients is mainly related to a deficiency in the synthesis of endogenous EPO [7]. Therefore, the use of recombinant human EPO represents a logical and commonly used treatment for this disorder. EPO has been shown to improve QOL, exercise capacity, cognitive function, and sleep disturbances and ameliorate left ventricular hypertrophy, which is a major contributor to cardiac mortality and morbidity in patients with end-stage renal disease (ESRD) [8–13]. Most patients receiving hemodialysis (HD) for ESRD currently receive EPO for anemia treatment. Anemia from EPO deficiency is a common complication of chronic kidney disease (CKD). It can be treated with EPO administration, red blood cell transfusion, or a combination of both [14]. But the widely accepted use in patients with anemia is EPO administration. Early studies found that EPO reduced the need for transfusions and improved the QOL in patients with CKD, when compared with not using EPO [15,16]. EPO is routinely used to treat anemia of CKD, especially in patients who need dialysis. The goal of therapy is to achieve specific Hb target levels. Higher doses of EPO, however, are being used to attain higher target levels without evidence of corresponding clinical benefit and possibly resulting in harm. It is remarkable that the three largest studies and a meta-analysis, involving 3268 subjects, have had a very consistent outcome, a 21% to 48% increased risk for mortality in the higher Hb target group, which in each study nearly reached statistical significance [11,17–19]. The Food and Drug Administration in the United States suggests that increasing the hemoglobin level to more

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than 12 g/dl may be associated with increased morbidity and mortality and that the benefits of these drugs have not been well documented and this would imply that the Food and Drug Administration asserts an Hb target level of only 10 g/dl because this level is far from the range of demonstrated risk [20] while the cost consequences of using EPO to achieve higher Hb targets is increasing. In 2007, the Food and Drug Administration ruled that minimization of blood transfusions and low red blood cell levels were the predominant indications for EPO in anemic patients with CKD; regarding low red blood cell levels, the recommendation of Hb levels is 10 to 12 g/dl [21]. Nowadays, target Hb levels in CKD remain uncertain because Hb target levels above 13 g/dl have been associated with both benefit (QOL) and harm (cardiovascular events) [22]. Many HD patients receive EPO for their anemia as a part of routine therapy. Because EPO is an expensive therapy, it has created an economic burden onto the health care system of every country including a developing country such as Thailand. The purpose of this study was to evaluate the cost-effectiveness of EPO use for different target Hb levels at the resources of a developing country.

Methods

A Markov model was constructed to estimate the incremental costs and QALY gains associated with EPO treatment for maintaining Hb levels of more than 9 to 10, more than 10 to 11, more than 11 to 12, and more than 12 g/dl compared with 9 g/dl or less. The study adopted a societal perspective. The results were presented in terms of incremental costs (US $), incremental quality-adjusted life-years (QALYs) gained, and incremental cost-effectiveness ratio (ICER). The HD patients may be alive with a cardiovascular (CV) event or a noncardiovascular (nCV) event such as catheter-related infections and then they have a chance of dying from a CV event (death from the CV state) or an nCV event (death from the nCV state). So, the Markov model was viewed as four states: dead from CV, dead from nCV, alive with HD, and alive with hemodialysis and cardiovascular disease (HDCV), as shown in Figure 1. The four health states were defined by the solid line ovals and occurred in each Hb level (five Hb levels such as ≤9, >9–10, >10–11, >11–12, and >12 g/dl). A fixed 1-year cycle length was assigned. The time horizon of the analysis was the lifetime of the patient.

In this Markov model, we classified HD patients into two groups: 1) the patients who were alive with HD (the HD state) and 2) the patients who were alive with HDCV treatment (the HDCV state). When the HD state's patients moved to the HDCV state (arrow no. 1), they could not move back to the HD state because they would be treated CV forever. The HD state's patients, however, stayed in the HD state if no event occurred (dotted-line arrow no. 2) or if they successfully completed the nCV treatment (arrow no. 3). When the nCV treatment was not successful, they moved to the state of death from the nCV event (arrow no. 4). The HDCV patients stayed in the HDCV state when no event occurred (dotted-line arrow no. 5) or they successfully completed the nCV treatment (arrow no. 6). When the nCV or CV treatment was not successful, they moved to the state of death from the nCV event (arrow no. 7) or the CV event (arrow no. 8). It was assumed that once the patients have HD or HDCV, they would continue to hemodialyse until dead (absorbing health state). Costs and QALYs gained were calculated as patients went through the model. The moving of any state was assumed to be independent of their moving Hb level. The movement between each state was determined by probabilities that were obtained from randomized controlled trials (RCTs) and systematic reviews.

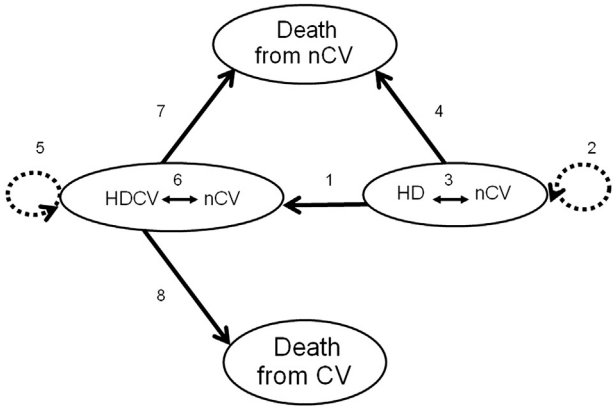

Fig. 1 – Schematic representation of Markov model. CV, cardiovascular; nCV, noncardiovascular; HD, hemodialysis; HDCV, hemodialysis and cardiovascular disease.

Transitional Probability Data

Transitional probabilities used in this study were obtained mainly from systematic review of the literature using the PubMed database, the National Coordinating Centre for Health Technology Assessment, the Cochrane library, and the ClinicalTrials.gov Web site. Search dates were between January 1, 1966, and December 31, 2009. All searches included the keywords and corresponding MeSH terms for erythropoietin, kidney disease, renal disease, hemodialysis, randomized controlled trial (RCTs), meta-analysis, and practice guideline. These studies included the studies of efficacy of EPO (e.g., erythropoietin beta, and alfa); the methodology of the studies was RCTs, meta-analysis of RCTs, which assessed the effects of targeting different Hb concentrations when treating patients with anemia caused by CKD with EPO, and the targeted patients were older than 18 years. These studies excluded nonrandomized trials or RCTs that were evaluating other interventions such as subcutaneous versus intravenous EPO treatment for anemia of CKD; outcomes such as blood viscosity and hematopoietic progenitor cell assays were reported.

We identified 277 potentially eligible articles, 204 of which were excluded because these were not RCTs. Seventy-three RCTs consisted of 22 studies that assessed the dose and route of administration, 15 hematological and hemodynamic effects studies, and 21 other intervention studies, that is, nutritional supplement. Thirteen RCTs and 2 meta-analyses of RCTs of EPO in CKD were full articles but only 4 RCTs [11,12,23,24] met the specified inclusion criteria. These studies were conducted in Canada and Europe. There was no study conducted in Thailand or Asia. From the clinical trial, we derived the compound mortality rate and then we calculated the disease-specific mortality rate using the following formula:

$$\mu_C = \mu_D + \mu_{ASR}$$

where μ_D is the disease-specific excess mortality rate (fixed rate), μ_C is the compound mortality rate derived from the study in the literature, and μ_{ASR} is the age-, sex-, race-adjusted mortality rate.

$$\mu_{ASR} = 1/LE_{ASR}$$

where LE_{ASR} (ASR is the age-, sex-, race-adjusted life expectancy) is the life expectancy of the Thai general population classified by age group (derived from Life Table of Vital Statistics Thailand 2006 [25]).

When we knew the mortality rate for different ages, we converted the rate to probability (P), assuming that an event occurs at a constant rate (r) over a time period between time zero to sometime beyond, such as the time period between the first year and the fifth year is 4 (t):

$$P = 1\text{–}e^{-\text{rate}}$$