A Review of Cost-Effectiveness Analyses for Anemia in Chronic Kidney Disease

Poster #188

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PRESENTED AT NKF SPRING CLINICAL MEETINGS 2019

INTRODUCTION

- Anemia is a common and serious complication of chronic kidney disease (CKD), driven predominantly by renal erythropoietin and/or iron deficiency, which decreases hemoglobin (Hb) levels, and contributes to increased morbidity and mortality[1,2]
- Kidney Disease: Improving Global Outcomes, or KDIGO, treatment guidelines recommend patients be treated with erythropoietin-stimulating agents (ESA), oral (PO) or intravenous (IV) iron, and/or red blood cell transfusion (RBCT), depending on the patient's current disease features and treatment history[3]
- The economic implications of these treatment decisions, however, remains uncertain
  - Pharmacoeconomic models are tools used to assess the value provided by interventions, and to estimate the economic implications of various treatment decisions
  - Model design, and complexity, are often related to many factors, including the:
    (1) research question;
    (2) disease pathway; and
    (3) availability of resources (e.g., clinical and economic evidence)

OBJECTIVE

- We conducted a review of published cost-effectiveness analysis (CEA) models to examine the methods and results of studies used to evaluate the economic value of treatment options for anemia in CKD

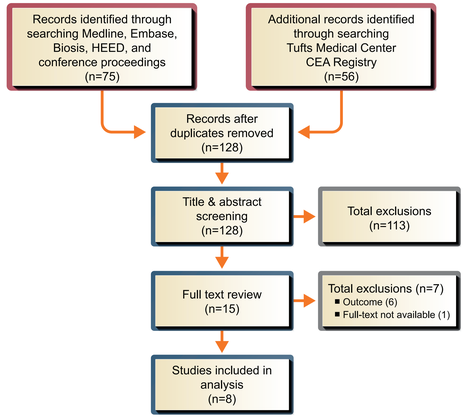
METHODS

- We searched the Tufts CEA Registry, Health Economic Evaluations Database (HEED), Medline, Embase, Biosis, and conference proceedings to identify CEAs of CKD anemia treatment published January 2000 to May 2018
  - Conference proceedings from American Society of Nephrology (ASN), European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), and Academy of Managed Care Pharmacy (AMCP)
- Searches incorporated keywords and subject headings specific to: (1) anemia; (2) CKD, including dialysis and end-stage renal disease (ESRD); and (3) CEA
- We identified and reviewed papers that met our inclusion criteria:
  - **Population:** adults (aged ≥18 years) with CKD and anemia
  - **Intervention:** pharmacologic and non-pharmacologic treatment
  - **Outcomes:** incremental cost-effectiveness ratio (ICER)
  - **Other criteria:** English language, publications that included complete description of the methods and results
- Data related to study methods including population characteristics, interventions, modeling approach, parameter and input sources, and model outcomes were abstracted

RESULTS

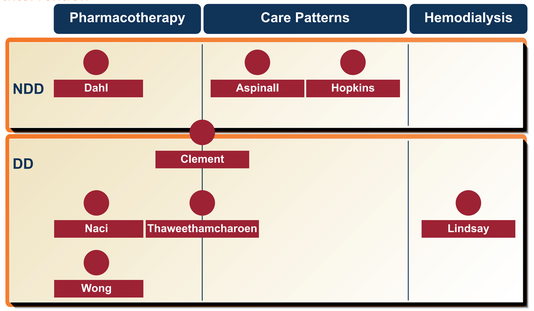
- 131 studies were identified, of which 8 eligible studies comprised the evidence base (**Figure 1**)

Figure 1. PRISMA Diagram: Literature Review of Cost-Effectiveness Analyses in CKD-Anemia



- Four models focused on dialysis-dependent (DD) patients, three on non-DD (NDD) patients, and one on both DD and NDD (**Table 1; Figure 2**)
- Interventions evaluated in models were related to pharmacotherapy, care patterns or healthcare delivery, or hemodialysis (**Table 1; Figure 2**)
  - Pharmacotherapies included ESA, and iron administered via IV, PO, or parenteral (PAR) routes
  - Care patterns involved use of different Hb target levels or novel disease management strategies (e.g., pharmacist-managed ESA)
  - Hemodialysis (HD) varied by timing and frequency (i.e., nocturnal, daily short-hour, or three-times weekly conventional)
- Models were designed from the perspectives of four countries: United States (3); Canada (3); Australia (1); and Thailand (1)
- The commercial payer perspective was adopted in four models, and the government payer perspective (only direct costs considered) and societal perspective were adopted in two and two models, respectively
  - Models developed from the societal perspective incorporated direct medical costs along with direct nonmedical costs and/or work productivity (i.e., patient, caregiver)
- Five CEAs were Markov models that estimated clinicoeconomic outcomes for time horizons spanning from five years to a lifetime
  - NDD health states defined by achieving the Hb target and/or progression to ESRD
  - DD health states defined by dialysis status (i.e., on or off), and/or incidence of cardiovascular disease, and renal transplant
- Two models were CEAs conducted alongside prospective studies (piggyback cost analysis), and another was a trial-based analysis conducted alongside pooled data from two identical randomized clinical trials (RCTs); these analyses did not model outcomes past the study time horizon
  - Economic outcomes are derived by applying cost tolls directly to the utilization of healthcare services observed in these studies and outcomes are calculated over a shorter time horizon (i.e., five weeks to two years)
- Studies most often reported results that favored the newer intervention, but not all interventions were cost-effective with respect to traditional cost-effectiveness thresholds
  - IV and PAR iron were shown to provide better economic outcomes relative to PO iron, using different approaches
    - Dahl, et al. (2017)[4] report the benefit of IV iron (± ESA) in terms of cost per unit increase in Hb, relative to PO iron (± ESA)
    - Wong, et al. (2013)[5] report the benefit of PAR iron in in terms of incremental cost-effectiveness ratio (cost per quality-adjusted life year [QALY] and cost per life year [LY])
  - Naci, et al. (2012)[6] report ESA is cost-effective relative to monthly RBCT; while Clement, et al. (2010)[7] and Thaweethamcharoen, et al. (2014)[8] report ESA is more cost-effective when using lower Hb targets
  - Both nurse-nephrologist coordinated care and pharmacist-managed ESA were cost-effective, relative to standard of care, in models by Hopkins, et al. (2011)[9] and Aspinall, et al. (2013)[10], respectively
  - In a comparison of HD types, Lindsay, et al. (2004)[11] report nocturnal and daily short-hour are both cost-effective relative to conventional HD (three times per week)

Figure 2. Overview of CEAs Stratified by Population and Type of Intervention



- These economic analyses captured the clinical and economic benefits of anemia management in a variety of ways:
  - Improved clinical outcomes and survival;
  - Increased efficiency in healthcare resource utilization;
  - Increased model-time spent in transition states with higher utility values; and/or
  - Improved work productivity for patient and/or caregiver

Table 1. Characteristics and Findings of Cost-effectiveness Analyses for Treatment of CKD Anemia

	Author (Year)	Population	Interventions	Model Design	Time Horizon	Study Perspective	Primary Study Finding *Economic Benefit Related to Hb Management*
	Dahl (2017)[4]	NDD	- IV iron (± ESA); - PO iron (± ESA)	Trial-based analysis[a]	5 wks	Commercial payer	The cost per unit increase in hemoglobin (g/dl) is lower with IV iron (±ESA) versus PO iron (±ESA). *Change in mean Hb the highest with IV iron (±ESA), offsetting treatment-related costs.*
	Aspinall (2013)[10]	NDD	- Pharmacist-managed ESA; - Standard ESA care	Markov model (1-mo cycles)	5 yrs	Gov't payer	Pharmacist-managed ESA care is economically dominant (i.e., lower costs and improved effectiveness). *Costs related to increased patient monitoring were offset by lower ESA doses being needed and reduced risk of cardiovascular events.*
	Hopkins (2011)[9]	NDD	- Nurse-nephrologist-coordinated care[a]; - Standard care	Piggyback cost analysis (RCT)	2 yrs	Societal[a]	Nurse-nephrologist coordinated care is economically dominant. *Costs for utilization related to increased patient monitoring is offset by reduced frequency of ER visits and hospitalization, improved work productivity and decreased need for assistance with daily activities.*
	Clement (2010)[7]	NDD-DD	- ESA targets[b]; - No ESA use	Markov model (1-yr cycles)	Lifetime	Commercial payer	The cost per QALY of ESA using any target exceeds $100k (vs no ESA); targeting low-to-intermediate Hb targets (9-12 g/dl) is more cost-effective relative to a higher Hb target (>12 g/dl). *Hb control improved clinical outcomes (e.g., mortality, dialysis initiation) and quality of life (i.e., utility values); costs are higher with lower Hb targets, however, yields largest improvement in QALYs observed due to lowest mortality risk.*
	Thaweetham-charoen (2011)[8]	DD	- ESA targets[c]	Markov model (1-yr cycles)	Lifetime	Societal[f]	Hb targets >9 g/dl are cost-effective relative to targeting ≤9 g/dl. Higher targets produce increases in QALYs, but with additional costs. *Improved quality of life with the use of higher Hb controls, however, there is a need to balance this benefit with the costs and treatment risks.*
	Naci (2012)[6]	DD	- ESA; - RBCT	Markov model (1-yr cycles)	10 yrs	Commercial payer	ESA use is cost-effective for treatment of anemia in CKD (vs RBCT). *Improved quality of life (i.e., utility values) when Hb is well-managed. Cost of ESA largely offset by frequent transfusions and need for iron chelation therapy.*
	Wong (2013)[5]	DD	- PAR iron; - PO iron	Markov model (1-yr cycles)	Lifetime	Gov't payer	PAR iron (+ESA) was more cost-effective at hemoglobin targets between 9.5 and 12 g/dL as compared to oral iron (+ESA). *PAR iron improved the likelihood of reaching Hb targets which resulted in reduced ESA doses, improved quality of life (i.e., utility values), and reduced the risk of all-cause mortality.*
	Lindsay (2004)[11]	DD	- Nocturnal HD; - Short-hour HD (qd); - Conventional HD (3qw)	Piggyback cost analysis (cohort study)	18 mos	Commercial payer	Nocturnal and daily short-hours HD were cost-saving compared to conventional HD, while providing added clinical benefit. *Hb consistent across comparator arms with the use of iron and/or ESA.*

3qw, three times per week; DD, dialysis-dependent; ESA, erythropoietin stimulating agent; Hb, hemoglobin; HCP, health care payer; HD, hemodialysis; IV, intravenous; mo(s), months; NDD, non-dialysis-dependent; PAR, parenteral; PO, oral; QALY, quality adjusted life year; qd, every day; RBCT, red blood cell transfusion; RCT, randomized controlled trial; wk(s), week(s); yr(s), year(s)
[a] Nurse-nephrologist coordinated care for goal-directed therapy for common comorbidities, including: blood pressure, dyslipidemia, and anemia
[b] ESA treatment to the following hemoglobin targets: low (9-10.9 g/dl); intermediate (11-12 g/dl); high (>12 g/dl)
[c] ESA treatment to the following hemoglobin targets: <9 g/dl; >10-11 g/dl; >11-12 g/dl; >12 g/dl
[d] Cost tolls applied to outcomes from two identical RCTs
[e] Model includes direct non-medical costs (caregiver out of pocket costs for food, transportation, and accommodations) and patient income or productivity loss
[f] Model includes income or productivity loss experienced by patients and caregivers.

DISCUSSION AND CONCLUSIONS

- This is the first published literature review that we are aware of that describes modeling approaches and results from published CEAs of various treatment approaches in CKD anemia.
- Published economic models have shown the clinicoeconomic benefit of anemia treatment to the patient and caregiver, healthcare provider, and payer.
- Substantial heterogeneity exists with respect to modeling approaches; this is likely a result of differing populations and interventions, and clinical evidence available at the time the model was developed.
- Results mostly supported the use of newer interventions, and support the value of innovation in the CKD anemia treatment paradigm.
- The key strength to our approach was the inclusion of a variety of publication databases for searches, including those containing conference proceedings; however, none were included in the evidence base as methods and/or results were not fully described.
- Future reviews should also consider including reports from established health technology assessment (HTA) agencies such as National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), as well as newly established HTAs like the multinational regional HTA network (RedETSA) in Latin America, Chuikyo in Japan and ICER in the US.

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Acknowledgments

This research was supported by Otsuka Pharmaceutical Development & Commercialization, Inc. and Akebia Therapeutics, Inc.

Disclosures

TL, NM, and FB are employees of Tufts Medical Center, Center for the Evaluation of Value and Risk. SM and MS are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. GS is an employee of Akebia Therapeutics, Inc., where AB was employed during the time the research was completed.

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