Treatments for Anemia in Chronic Kidney Disease

Revised Background and Scope
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Background

Anemia is described as "a condition in which the number of red blood cells or their oxygen-carrying capacity is insufficient to meet physiological needs."[1] In anemia, insufficient numbers of circulating red blood cells or inadequate quantities of iron or functional hemoglobin (Hb) are available to transport and release oxygen to tissues. Anemia is common in patients with chronic kidney disease (CKD). The World Health Organization and the 2012 Kidney Disease Improving Global Outcomes guidelines define anemia as an Hb level of <12 g/dL (grams per deciliter) in females and <13 g/dL in adult males.[2,3] However, this definition does not provide goals of treatment for different patient groups.

The definition and classification of CKD was established and endorsed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative and the international Kidney Disease Improving Global Outcomes guideline group.[3] Decreased kidney function refers to a decrease in glomerular filtration rate (GFR), which is usually estimated using serum creatinine and one of several available equations.[4,5] This definition is widely accepted and used among patients, clinicians, researchers, and regulatory agencies. Patients who are diagnosed with CKD can be categorized into different stages according to the cause, their GFR (five G-stages: I, II, III, IV, and V), and the amount of albumin or protein in the urine (three A-stages: 1, 2, and 3). Additionally, patients with CKD can advance from being dialysis independent (DI-CKD) to end-stage kidney disease (ESKD), which is defined as severely reduced kidney function or treatment with dialysis (dialysis dependent [DD-CKD]) or transplantation. Risk factors for CKD include genetic or sociodemographic predisposition, or the presence of diseases that can initiate and propagate kidney disease such as diabetes and hypertension. CKD is a worldwide public health problem. The number of patients enrolled in the ESKD Medicare-funded program has increased from approximately 10,000 beneficiaries in 1973 to 703,243 as of 2015.[6]

Anemia in patients with CKD can be due to reduced production of erythropoietin by the kidneys, iron deficiency, inflammation, and the accumulation of uremic toxins that leads to shortened red blood cell survival.[7-9] Anemia causes many of the symptoms associated with CKD such as fatigue, depression, breathlessness, and reduced exercise tolerance. Anemia is also associated with increased morbidity and undesirable outcomes including mortality and hospitalizations.[10-13] In

patients with DI-CKD, the prevalence of anemia increases with decline in kidney function and advancing stages of CKD.[14-16] For example, based on over 12,000 participants in the National Health and Nutrition Examination Survey, the prevalence of anemia (Hb <13 g/dL in men and <12 g/dL in women) increased from 8.4% at CKD stage G-I to 53.4% at CKD stage G-V.[17] Nearly all patients with DD-CKD have anemia that must be managed.

Managing anemia in patients with CKD requires evaluating adequacy of iron stores. Additionally, up until now, managing anemia involved the use of recombinant erythropoietin and its synthetic derivatives (epoetin alfa, epoetin beta, darbepoetin alfa, methoxy polyethylene glycol-epoetin beta; collectively known as erythropoiesis-stimulating agents [ESAs]). Recombinant human erythropoietin was developed in the late 1980s.[18] In the pre-ESA era, blood transfusion—with all of its potential risks including iron overload, antibody formation against blood cell antigens, sensitization to transplant antigens, and transfusion-related infections like viral hepatitis—was the main management strategy among CKD patients with anemia. The United States (US) Food and Drug Administration (FDA) approved recombinant human erythropoietin for the treatment of anemia in DD-CKD in 1989 and broadened approval to include anemia in DI-CKD in 1990. ESAs are administered intravenously or subcutaneously. After FDA approval, there was a rapid and widespread uptake of ESA use in CKD patients, which was supported by recommendations in clinical practice guidelines.[19] However, despite the association between anemia and higher mortality in uncontrolled studies, subsequent evidence based on multiple randomized controlled trials emerged and showed that correction of anemia and maintenance of Hb to near normal levels with ESAs increased mortality and cardiovascular events without consistently improving quality of life.[20-23]

Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) enzyme inhibitors have emerged as a new class of agents for the management of anemia in CKD. These agents work by stabilizing the HIF complex and stimulating endogenous erythropoietin production in patients with DI-CKD and DD-CKD. HIF-PH inhibitors are administered orally, which may be favorable for some patients, especially those who are not yet on dialysis. By inducing considerably lower, but more consistent, erythropoietin levels compared to ESAs, it is plausible that HIF-PH inhibitors may be associated with fewer adverse cardiovascular events. There are four HIF-PH inhibitors undergoing Phase II and III clinical trials in the US including roxadustat, vadadustat, daprodustat, and molidustat. This review will focus on roxadustat as it is the only agent that has been submitted to the FDA for consideration of approval.

Stakeholder Input

This scoping document was developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders, open input submissions from the public, and public comments received. For instance, in response to feedback, we added additional outcomes such as CKD progression as assessed by eGFR and use of rescue therapy. ICER looks forward to continued engagement with stakeholders throughout its review.

Report Aim

This project will evaluate the health and economic outcomes of roxadustat for anemia in CKD. The ICER Value Assessment Framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms—including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs—are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for this review will be adults with anemia associated with CKD. Data permitting, we will consider evidence across two relevant populations of patients:

1. Patients with DI-CKD
    - In population one, we will plan to evaluate subgroups of patients defined by stages of CKD: G-stages III, IV, and V.
2. Patients with DD-CKD
    - In population two, we will plan to evaluate a subgroup of patients newly initiated on dialysis.

Other subgroups of interest may be defined according to iron status, inflammation status and ESA-hyporesponsiveness, presence of cardiovascular disease, or cancer.

Interventions

The intervention of interest is roxadustat (AstraZeneca and FibroGen).

Comparators

We intend to compare roxadustat to:

- Darbepoetin alfa (Aranesp®, Amgen)
- Epoetin alfa (Epogen®, Amgen; Procrit®, Janssen)
- Methoxy polyethylene glycol-epoetin beta (Mircera®, Roche)
- Usual care (estimated by placebo arms of clinical trials)

Outcomes

The outcomes of interest are described in the list below.

- Patient-important outcomes
    - All-cause mortality
    - Cardiovascular mortality
    - Stroke
    - Myocardial infarction
    - Unstable angina
    - Heart failure
    - Hospitalization
    - Blood transfusion
    - Rescue therapy

    - ESKD
    - Health-related quality of life
    - Improvement in symptoms or function (e.g., fatigue, dyspnea)
    - Adverse events including:
        - Serious adverse events
        - Treatment-emergent adverse events
        - Adverse events leading to treatment discontinuation
- Other outcomes
    - Anemia (as assessed by Hb and/or hematocrit)
    - Measures of iron storage and availability
    - Measures of inflammation
    - Lipid levels
    - CKD progression (as assessed by eGFR)

Timing

Evidence on intervention effectiveness and evidence on harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the US.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table on the following page.

Table 1.2. Potential Other Benefits or Disadvantages and Contextual Considerations

1 (Suggests Lower Value)	2 (Intermediate)	3 (Suggests Higher Value)
Uncertainty or overly favorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too optimistic.		Uncertainty or overly unfavorable model assumptions creates significant risk that base-case cost-effectiveness estimates are too pessimistic.
Very similar mechanism of action to that of other active treatments.		New mechanism of action compared to that of other active treatments.
Delivery mechanism or relative complexity of regimen likely to lead to much lower real-world adherence and worse outcomes relative to an active comparator than estimated from clinical trials.		Delivery mechanism or relative simplicity of regimen likely to result in much higher real-world adherence and better outcomes relative to an active comparator than estimated from clinical trials.
The intervention offers no special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.		The intervention offers special advantages to patients by virtue of presenting an option with a notably different balance or timing of risks and benefits.
This intervention will not differentially benefit a historically disadvantaged or underserved community.		This intervention will differentially benefit a historically disadvantaged or underserved community.
Small health loss without this treatment as measured by absolute QALY shortfall.		Substantial health loss without this treatment as measured by absolute QALY shortfall.
Small health loss without this treatment as measured by proportional QALY shortfall.		Substantial health loss without this treatment as measured by proportional QALY shortfall.
Will not significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.		Will significantly reduce the negative impact of the condition on family and caregivers vs. the comparator.
Will not have a significant impact on improving return to work and/or overall productivity vs. the comparator.		Will have a significant impact on improving return to work and/or overall productivity vs. the comparator.
Other		Other

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost effectiveness of roxadustat relative to relevant comparator treatments. The model structure will be based in part on a literature review of prior published models of CKD and anemia in CKD.[24,25] The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Unique payment arrangements exist for the treatment of DD-CKD such as bundled payment systems. An additional scenario analysis may be undertaken to estimate the cost of roxadustat and comparators in these unique payment arrangements. Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case if the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. Two target populations will be considered: those with DI-CKD (CKD G-stages III, IV, and V) and DD-CKD. Depending on data availability, we may consider subgroups of patients who are ESA-hyporesponsive, patients with cardiovascular disease, or those with comorbid cancer. The anticipated comparators to roxadustat are ESAs in both the DI-CKD population and DD-CKD population, although the market share of specific ESAs used within these two populations may differ.[26]

The model will likely consist of health states based on CKD stages (DI-CKD G-stages III, IV, and V and DD-CKD, post-transplant, and death) with an overlay of a change from baseline in mean Hb level and proportion of patients within Hb level strata in each of the CKD stages. Patients will transition between states during predetermined cycles over a lifetime time horizon, modeling patients from treatment initiation until death, with a 3% discount rate for costs and outcomes. In addition, cost effectiveness will be estimated for shorter time horizons (e.g., five years). It is anticipated that drugs to treat anemia in CKD will not modify the underlying course of disease in CKD. As such, the underlying transitions between CKD stages and death will be based on published models of CKD.[24] Reduced risk of CKD progression may be considered if substantive data exist that demonstrate reduced risk of CKD progression with roxadustat or ESAs. Utility will be based on CKD stage with an adjustment for improvement in Hb. Data permitting, the model will also consider administration costs, use of intravenous iron, adverse events, blood transfusions, major adverse cardiovascular events, and risk of mortality.[27,28]

Key model inputs will include clinical probabilities, health state utilities, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using the change from baseline Hb level from a network meta-analysis of roxadustat and comparator agents (if feasible to conduct a network meta-analysis) or from outcomes of the roxadustat Phase III trials and pivotal Phase III trials of comparator agents.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events, and direct medical costs. The health outcome of each intervention will be evaluated in terms of blood transfusions avoided, major adverse cardiovascular events avoided, life-years gained, quality-adjusted life years (QALY) gained, and equal value of life-years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs including but not limited to drug costs (including dose escalation among hyporesponsive patients), costs related to drug administration, drug monitoring, condition-related care, transfusion of blood products, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLYG, cost per life-year gained, and cost per blood transfusion avoided.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

As described in its Value Assessment Framework for 2020-2023, ICER will include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services. These services are ones that would not be directly affected by roxadustat (e.g., reduction in blood transfusion), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of CKD beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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