Treatments for Anemia in Chronic Kidney Disease: Effectiveness and Value

Executive Summary

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Prepared for

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Anemia is common in patients with chronic kidney disease (CKD), and typically becomes more prevalent with decreasing hemoglobin (Hb) levels as CKD progresses from dialysis-independent CKD (DI-CKD) to dialysis-dependent CKD (DD-CKD).[1-4] Nearly all patients with DD-CKD have anemia that must be managed. 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 (RBC) survival.[5-7]

Prior to the mid-1980s, blood transfusion was the main strategy for managing anemia in CKD. In the late 1980s, recombinant human erythropoietin was developed,[8] and the use of erythropoietin and related compounds collectively known as erythropoiesis-stimulating agents (ESAs) dramatically reduced the need for transfusions.[9] ESAs may be injected subcutaneously at home or infused during dialysis, and so different regimens may be chosen based on need for dialysis and/or intravenous (IV) iron, and based on whether patients receive home peritoneal dialysis, home hemodialysis, or in-center dialysis. Despite the association between anemia and higher mortality in uncontrolled studies, subsequent evidence based on multiple randomized controlled trials (RCTs) 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.[10-13]

Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors have emerged as a new class of orally-administered agents for the management of anemia in CKD. They induce considerably lower, but more consistent, erythropoietin levels compared to ESAs and it has been hypothesized that they could cause fewer adverse cardiovascular events than ESAs.[14,15] The HIF-PH inhibitor roxadustat (AstraZeneca) is under review by the Food and Drug Administration (FDA).[16]

In speaking with patients and patient organizations, we heard about the importance that patients place on autonomy and the ability to maintain activities of daily living. Most patients described their experiences with fatigue. We heard that among those patients with anemia, some feel better after their anemia is treated and some do not. We also heard concerns about becoming sensitized through transfusions, reducing the chance of finding an appropriate kidney for transplant.

ESAs and roxadustat can both be dose-adjusted to correct anemia to a given degree and reduce the need for transfusions,[17] although patients receiving ESAs frequently also need to receive IV iron. As such, a primary focus of our review looked at the relative safety of these therapies as assessed by all-cause mortality, myocardial infarction (MI), and stroke (the composite "MACE" in the roxadustat trials), and additional endpoints of hospitalization for unstable angina or heart failure ("MACE+").

In the DI-CKD population, we identified three key published Phase III randomized controlled trials (RCTs) of roxadustat[18-20] and one key unpublished Phase III RCT of roxadustat.[21] A pooled analysis of the placebo-controlled trials reported no statistically significant difference in all-cause mortality with roxadustat (hazard ratio [HR]: 1.06; 95% confidence interval [CI]: 0.91 to 1.23), however this included many patients no longer on treatment, which could bias toward no effect. A meta-analysis of relative risks (RRs) suggested a possible increase in mortality with roxadustat (RR: 1.15, 95% CI: 1.00 to 1.33), however discontinuations could have biased this result toward overestimating any such risk.[17] In support of this possibility, the HR for mortality on treatment was published for one trial and was 0.96, compared with a RR of 1.17 from that same trial.[20,22,23] In the trial comparing roxadustat with an ESA, there were no statistically significant differences in the risk of MACE (HR: 0.81, CI: 0.52 to 1.25), MACE+ (HR: 0.90, CI: 0.61 to 1.32), or all-cause mortality (HR: 0.83, CI: 0.50 to 1.38).[21]

In the DD-CKD population, we also identified four key unpublished Phase III RCTs comparing roxadustat with ESAs.[22,24-26] A pooled analysis of three of these trials reported that roxadustat was not different from ESAs in the risk of first MACE (HR: 0.96, CI: 0.82 to 1.13) and all-cause mortality (HR: 0.96, CI: 0.79 to 1.17), however roxadustat reduced the risk of MACE+ (HR: 0.85, CI: 0.74 to 0.98).[17] We used available data from all four trials to perform a meta-analysis of all-cause mortality and found no statistically significant difference (risk ratio [RR]: 1.05, CI: 0.88 to 1.26). The need for IV iron supplementation was reduced with roxadustat across all trials.

In summary, in the DI-CKD population, roxadustat reduces the need for transfusions compared to usual care, but we have substantial uncertainty about the effects of roxadustat on all-cause mortality and have rated the evidence *insufficient* ("*I*") for this comparison. Compared with ESAs, the confidence intervals around MACE and MACE+ include the possibilities of clinically important harms and benefits and, as such, we have rated the evidence *insufficient* (*I*) for this comparison as well. For similar reasons, in the DD-CKD population, we have *insufficient* evidence (*I*) for the comparison between roxadustat and ESAs.

Votes of the California Technology Assessment Forum (CTAF) at the Public Meeting on February 11, 2021 agreed with the above assessments: the CTAF Panel unanimously voted that evidence was not adequate to demonstrate to demonstrate the superiority of roxadustat over usual care in the DI-CKD population or to distinguish the net health benefit in comparison with ESAs in the DI- and DD-CKD populations.

In economic modeling, we assumed a placeholder price for roxadustat of $6,500 per year using analysts' estimates. In the DI-CKD population, given the lack of statistical significance, we assumed no difference in MACE+ events, and roxadustat slightly reduced lifetime costs with no effect on quality-adjusted life years (QALYs) or equal-value life years (evLYs) compared with ESAs. In the DD-CKD population, we used point estimates of individual MACE+ outcomes given the statistical significance of the composite. The increased all-cause mortality estimate resulted in fewer QALYs

and evLYs with roxadustat. Roxadustat treatment in the DD-CKD population had small reductions in lifetime costs both from a commercial and Medicare perspective, driven primarily by less time spent in CKD health states due to higher mortality rather than from improvements in patient outcomes.

The CTAF votes on potential other benefits and contextual considerations highlighted that roxadustat has a new mechanism of action and that its oral route of administration could improve real-world adherence compared with ESAs. CTAF also highlighted the large burden of illness of CKD.

There is currently insufficient evidence to compare roxadustat and ESAs. Roxadustat provides an oral option for treating anemia related to CKD and reduces the need for IV iron. Although it has been suggested to be a safer alternative to ESAs, the evidence does not currently confirm that conclusion. Cost effectiveness will depend on the manufacturer's price.

Themes and recommendations from the CTAF Public Meeting include:

- Given the level of uncertainty about the benefits versus harms and the long-term effect of using roxadustat compared to ESAs, we strongly suggest a mandate for a registry or other rapid and comprehensive post-marketing assessment.
- The manufacturer should not hold data in confidence from RCTs completed more than one to two years ago. The company has a responsibility to patients and clinicians to move these data into the public domain, to submit data rapidly for peer review in advance of regulatory approval, and to share these data in a transparent manner with groups seeking to assess the evidence to inform clinical practice and policy.
- If roxadustat gains regulatory approval, the manufacturer should price the drug in alignment with its demonstrated value, which at the current time is highly uncertain given the lack of clarity about overall mortality and cardiovascular outcomes. In this setting, with significant uncertainty of this magnitude, the manufacturer should set the price lower than treatments with more established evidence and wait until further evidence addresses the uncertainties before seeking a higher price.
- The manufacturer and researchers should avoid focusing primarily on Hb levels and the need for transfusion. Future research should expand outcomes measured to include patient-relevant outcomes such as quality of life, functional status, fatigue, overall cardiovascular events, and mortality in addition to the need for transfusion.

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