Variation in health plan coverage of ESAs for anemia due to chronic kidney disease

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What is already known about this subject

- Treatment for chronic kidney disease is influenced by patients' health plan drug coverage.
- Variations in plans' coverage policies may have implications for patients' access to erythropoiesis-stimulating agents.

What this study adds

- Health plans applied restrictions on coverage in over a quarter of policies, most often through step therapy protocols.
- Plans varied with respect to the types of evidence cited in coverage policies, but most plans showed a preference for randomized controlled trials and clinical or treatment guidelines.
- An understanding of the evidence health plans review for ESA coverage helps inform product manufacturers, physicians, and patients of the inputs that influence coverage decision making.

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ABSTRACT

BACKGROUND: Because health plans each issue their own policies, drug coverage can vary. This variation can result in patients having unequal access to treatment. In this study, we evaluate commercial health plans' coverage policies for erythropoiesis-stimulating agents (ESAs) for patients with anemia resulting from chronic kidney disease (CKD).

OBJECTIVES: To assess how a set of US commercial health plans cover ESAs for patients with anemia due to CKD. Our second objective was to examine the evidence that the plans reviewed when formulating their coverage policies.

METHODS: We used the Tufts Medical Center Specialty Drug and Evidence and Coverage Database to identify coverage policies issued by 17 of the largest US commercial health plans for ESAs. The following drugs were indicated for anemia due to CKD: darbepoetin alfa, methoxy polyethylene glycol-epoetin beta, epoetin alfa (available as two brands), and epoetin alfa-epbx. Coverage policies were current as of May 2019. We determined whether the health plans applied any restrictions, such as step therapy protocols or patient subgroup restrictions, in their coverage policies. We categorized the evidence that plans cited to support their policies into seven categories: randomized controlled trials (RCTs), real-world evidence (RWE) studies (studies based on data collected in a

real-world setting), other clinical studies (eg, single arm trials), systematic reviews and/or meta-analyses, clinical or treatment guidelines, health technology assessments, and economic evaluations.

RESULTS: We categorized 72.5% of coverage policies (58/80 policies) as equivalent to the FDA label and 27.5% (22/80 policies) as more restrictive. In restricted policies, plans most often applied step therapy protocols (18/22 policies), followed by prescriber requirements (4/22 policies), and patient subgroup restrictions (3/22 policies). Five health plans applied restrictions in at least half of their coverage policies; seven plans did not apply restrictions in any policy. Plans that cited evidence reviewed an average of 10 citations

across their ESA coverage policies, ranging from one to 29 studies. Plans varied with respect to the types of cited studies: at least 50% of evidence cited by five health plans was RCTs, while half or more of the evidence cited by four health plans was clinical or treatment guidelines.

CONCLUSIONS: Health plans varied in how they covered ESAs for patients with anemia due to CKD and in the evidence cited in their coverage policies. Inconsistencies in plans' coverage policies may have implications for patients' access to ESAs.

Chronic kidney disease (CKD) prevents kidneys from producing sufficient erythropoietin, which is essential for erythropoiesis (red blood cell production). Erythropoiesis-stimulating agents (ESAs) are a class of medications that stimulate the bone marrow to produce red blood cells and are used to treat anemia due to a variety of causes, including CKD. Anemia prevalence increases with CKD progression.¹

The Centers for Disease Control estimate that 37 million people in the United States have CKD, which is more common in those aged 65 years or older (38%) than those aged 45–64 years (13%) or 18–44 years.² Anemia prevalence in non-dialysis dependent (NDD)-CKD patients increases with age and is higher in older patients (50.1%; Medicare beneficiaries) than in younger patients (28.0%; commercially insured).³

Anemia due to CKD results in a large economic burden for patients and the health care system.⁴ Research has found that compared to non-anemic CKD patients, anemic patients were associated with an unadjusted incremental monthly cost increase of \$1,089.⁵ In NDD-CKD, anemia is a risk factor for increased hospitalizations and length of hospital stay.^{6,7}

The FDA approved epoetin alfa-epbx (Retacrit) on May 15, 2018, which is the first epoetin alfa biosimilar.⁸ Epoetin alfa-epbx is the fifth ESA, joining its reference products, epoetin alfa (a short-acting ESA available as two brands: Procrit and Epogen), and two long-acting ESAs, darbepoetin alfa (Aranesp), and methoxy polyethylene glycol-epoetin beta (Mircera).

Studies have highlighted variation in how US commercial plans cover specialty drugs, including drugs indicated for rheumatoid arthritis and multiple sclerosis.^{9,10} Emerging research has identified similar variation in how Medicare and commercial payers cover personalized medicine technologies, including multi-gene panels and sequencing tests.^{11–13} Research has found that health plans rarely cite the same clinical and economic evidence for certain drugs. In particular, evidence suggests that health plans

use RWE differently when formulating their drug coverage policies.^{15–17}

We build on this literature by evaluating a set of US commercial health plans' coverage policies for ESAs for anemia due to CKD. First, we examine the patient access criteria health plans' imposed in their coverage policies for ESAs for anemia due to CKD. Second, we determine the evidence that the health plans reported reviewing when formulating their ESA coverage policies.

Methods

DATA SOURCE

We used the Tufts Medical Center Specialty Drug and Evidence and Coverage (SPEC) Database for this research. The SPEC Database contains information on coverage policies for 292 specialty drugs issued by 17 of the largest US commercial health plans, including policies for the five available ESAs. SPEC includes coverage policies issued by 11 national and six regional health plans and comprises more than 150 million (>60%) commercially covered lives. Coverage policies, issued by health plans, describe the patient population eligible for a treatment and the evidence that health plans reported reviewing when formulating their policy. We describe the SPEC Database in previously published research.¹⁶ In brief, we obtained information in SPEC from the publicly available coverage policies' health plans posted on their websites. Researchers manually extracted this information from health plans' coverage policies and included it in the SPEC Database. SPEC includes details on coverage restrictions, such as step therapy protocols and patient subgroup restrictions. SPEC itemizes the evidence health plans cite in their coverage policies. At the time of this analysis, data in the SPEC Database was current as of May 2019 (one year post FDA approval of epoetin alfa-epbx).

We designated each coverage policy for a drug as “less restrictive,” “equivalent,” or “more restrictive” than the FDA label indication. “Less restrictive” means that the health plan covers the drug for a broader patient population than the FDA label indication; “equivalent” means that the plan covers the drug for the same patient population as the FDA label indication; and “more restrictive” means the plan places restrictions on coverage beyond the limits specified by the FDA label indication.

We categorized coverage restrictions into three plan requirements: patient subgroup restrictions (the plan required patients to meet certain clinical criteria, eg, to have symptoms of a particular severity), step therapy protocols (the plan required patients to fail an alternative therapy before accessing the drug), and prescriber

TABLE 1 Coverage of Erythropoiesis-Stimulating as First- or Second-Line Treatments

Plan	First-line short-acting ESAs	First-line long-acting ESAs	Second-line short-acting ESAs	Second-line long-acting ESAs
Plan 1	Epo-P	N/A	Epo-E, Epo-R	Darb-a, Epo-b
Plan 2	Epo-P	N/A	Epo-E	Darb-a, Epo-b
Plan 3	Epo-R	Darb-a, Epo-b	Epo-E, Epo-P	N/A
Plan 4	Epo-P, Epo-R	N/A	Epo-E	Darb-a, Epo-b
Plan 5	Epo-P, Epo-R	N/A	Epo-E	Darb-a
Plan 6	Epo-E, Epo-R	Darb-a	Epo-P	Epo-b
Plan 7	Epo-E, Epo-P, Epo-R	N/A	N/A	Darb-a, Epo-b
Plan 8	Epo-E, Epo-P, Epo-R	Darb-a, Epo-b	N/A	N/A
Plan 9	Epo-E, Epo-P, Epo-R	Darb-a, Epo-b	N/A	N/A
Plan 10	Epo-E, Epo-P, Epo-R	Darb-a, Epo-b	N/A	N/A
Plan 11	Epo-E, Epo-P, Epo-R	Darb-a, Epo-b	N/A	N/A
Plan 12	Epo-E, Epo-P, Epo-R	Darb-a, Epo-b	N/A	N/A
Plan 13	Epo-E, Epo-P	Darb-a	N/A	N/A
Plan 14	Epo-E, Epo-P	Darb-a, Epo-b	N/A	N/A
Plan 15	Epo-E, Epo-P, Epo-R	Darb-a, Epo-b	N/A	N/A
Plan 16	Epo-E, Epo-P, Epo-R	Darb-a, Epo-b	N/A	N/A
Plan 17	Epo-E, Epo-P, Epo-R	Darb-a, Epo-b	N/A	N/A

Notes: Information up to date as of May 15, 2019.

Darb-a=darbepoetin alfa; Epo-b=methoxy polyethylene glycol-epoetin beta; Epo-E=epoetin alfa (Epogen); Epo-P=epoetin alfa (Procrit); Epo-R=epoetin alfa-epbx (Retacrit); ESA=erythropoiesis-stimulating agent; N/A=health plan designated no erythropoiesis-stimulating agent to the given line of treatment.

requirements (the plan required that a certain type of physician prescribe the drug, eg, a nephrologist).

We categorized the evidence cited by health plans into the following categories: randomized controlled trials (RCTs), RWE studies (eg, those based on medical records), other clinical studies (clinical studies neither categorized as an RCT nor a RWE study), systematic reviews and meta-analyses, clinical or treatment guidelines, health technology assessments (technology assessments produced by national health technology assessment agencies), or economic evaluations (eg, cost-effectiveness analyses).

ANALYSES

We performed a set of descriptive analyses. First, we examined how health plans covered the ESAs for anemia due to CKD. Second, we examined and described the evidence that the plans cited in their coverage policies. We conducted the analyses using Stata Statistical Software: Release 14.¹⁸

Results

We identified 80 coverage policies for the five ESA products across the 17 health plans. All 17 plans issued coverage policies for darbepoetin alfa and both epoetin alfa products, 15 plans issued a policy for methoxy

polyethylene glycol-epoetin beta, and 14 plans issued a policy for epoetin alfa-epbx (Figure 2). Thirteen plans issued coverage policies for all five ESAs, three plans for four ESAs, and one plan for three ESAs (Table 1). Two plans did not issue a coverage policy for methoxy polyethylene glycol-epoetin beta, and three plans did not issue a coverage policy for epoetin alfa-epbx.

Of the 80 coverage policies, 58 (73%) were categorized as equivalent to the FDA label, and 22 (28%) as more restrictive than the FDA label. No coverage policies were less restrictive than the FDA label. With regard to the types of restrictions imposed, step therapy protocols were most common (18 of 22 restricted policies, 81%); followed by prescriber requirements, specifying the ESA be prescribed in consultation with, or by, a nephrologist in each instance (4 of 22 restricted policies, 18%); and then patient subgroup restrictions (3 of 22 restricted policies, 14%).

VARIATION IN HEALTH PLAN COVERAGE

Some health plans restricted coverage of the ESAs more frequently than others (Figure 1). Seven health plans restricted coverage of at least two ESAs, while eight health plans did not restrict coverage of any ESA.

Eight health plans designated all five ESAs as first-line treatments (ie, they did not impose step therapy protocols), one plan designated four ESAs as first-line treatment, four plans designated three ESAs as first-line treatments, two plans designated two ESAs first-line treatments, and two plans designated a single ESA (epoetin alfa [Procrit]) as the first-line treatment (Table 1).

Twelve plans designated both short and long-acting ESAs as first-line treatments. Five plans designated only short-acting ESAs as first-line

FIGURE 1 Variation in Health Plan Coverage of Erythropoiesis-Stimulating Agents for Patients with Anemia Due to Chronic Kidney Disease (N=80 Coverage Policies)

Notes: Number in parentheses equals the number of coverage policies issued by the health plan.

treatments; the plans required patients to first fail a short-acting ESA before granting access to a long-acting therapy.

Eleven plans covered all short-acting ESAs that they issued coverage policies for as first-line treatments. In contrast, six plans covered some short-acting ESAs as first-line treatments and some short-acting ESAs as second-line treatments. Eleven plans covered all long-acting ESAs that they issued coverage policies for as first-line treatments. One plan covered one long-acting ESA as first-line treatment (darbepoetin alfa) and one long-acting ESA as second-line treatment (methoxy polyethylene glycol-epoetin beta). Five plans only covered long-acting ESAs as second-line treatments.

VARIATION IN COVERAGE OF PARTICULAR ESAS

No ESA received identical coverage across all health plans. Plans imposed coverage restrictions more often for some

ESAs than for others (Figure 2). Plans imposed restrictions most often for methoxy polyethylene glycol-epoetin beta (7 of 15 policies, 47%) and least often for epoetin alfa-epbx (1 of 14 policies, 7%).

Health plans most often imposed step therapy protocols for methoxy polyethylene glycol-epoetin beta (7 of 15 policies, 47%) and least often for epoetin alfa-epbx (1 of 14 policies, 7%). Health plans imposed patient subgroup restrictions on only methoxy polyethylene glycol-epoetin beta (3 of 15 policies, 20%). One plan required that patients experience a reduction in their activities of daily living due to their disease, and two plans restricted coverage to adults. The FDA approved methoxy polyethylene glycol-epoetin beta for pediatric patients in some circumstances.¹⁹

FIGURE 2 Health Plan Coverage of Each Erythropoiesis-Stimulating Agent (N = 80 Coverage Policies)

Notes: Number in parentheses equals the number of health plans issuing a coverage policy for the drug. Coverage is more restrictive than the FDA label if the health plan applied a restriction in their decision, for example, the plan limits coverage to a subgroup of patients, or if the plan applies a step therapy protocol.

EPOETIN ALFA-EPBX COVERAGE

Thirteen of the fourteen health plans that issued a coverage policy for epoetin alfa-epbx did not impose any restrictions. One plan imposed a step therapy protocol with a requirement that patients first fail epoetin alfa (Procrit). The plan also imposed a prescriber requirement, requiring that the drug be prescribed by, or in consultation with, a nephrologist.

EVIDENCE PLANS CITED IN THEIR COVERAGE POLICIES

Health plans cited 62 unique pieces of evidence that met our criteria, with some evidence cited by multiple health plans. Systematic reviews or meta-analyses accounted for the largest proportion of cited evidence (35%, 22 of 62 citations), followed by RCTs (32%, 20 of 62 citations). Health plans rarely cited RWE studies (3%, 2 of 62 citations) or health technology assessments (3%, 2 of 62 citations).

VARIATION IN EVIDENCE BY HEALTH PLAN

Health plans varied in terms of the number of citations their policies included (Figure 3). Four health plans did not cite any evidence that met our criteria. Plans that cited evidence included an average of 10 citations across their coverage policies (range: one to 29 citations).

Half or more of the evidence cited by six health plans were RCTs; half or more of the evidence cited by five health plans were clinical or treatment guidelines. Only one health

plan cited RWE studies, and two plans cited health technology assessments.

VARIATION IN THE CITED EVIDENCE BY DRUG

Health plans collectively cited 45 unique sources in their coverage policies for epoetin alfa (Figure 4): 36 sources in their policies for darbepoetin alfa and 33 sources in their policies for methoxy polyethylene glycol-epoetin.

Overall, health plans cited RCTs, other clinical studies, clinical or treatment guidelines, and systematic reviews or meta-analyses for each ESA other than epoetin alfa-epbx. Plans cited RWE studies only for epoetin alfa and cited health technology assessments only for epoetin alfa and darbepoetin alfa. Plans cited RCTs in their policies for methoxy polyethylene glycol-epoetin beta (13 RCTs), epoetin alfa (10 RCTs), and darbepoetin alfa (nine RCTs).

Health plans cited only four studies for epoetin alfa-epbx, each of which was a systematic review or meta-analysis.

Discussion

We found that US commercial health plan coverage of ESAs for patients with anemia due to CKD can vary with respect to the coverage criteria they apply in their coverage policies. Some plans impose no restrictions on any of these agents, while others impose restrictions on all five ESAs. We found that no ESA was covered the same way by each health plan

FIGURE 3 Variation in Evidence Health Plans Cite in Their Coverage Policies for Erythropoiesis-Stimulating Agents for Patients with Anemia Due to Chronic Kidney Disease (N=62 Unique Studies)

Notes: Number in parentheses equals the number of publications that health plans cited in their coverage policies. Four health plans did not cite any evidence that met our inclusion criteria in their coverage policies.

in our sample. For each ESA, some health plans applied coverage restrictions, while other plans did not. We also found that some health plans covered only short-acting ESAs as first-line therapies, requiring patients to first fail a short-acting ESA before gaining access to a long-acting ESA.

These findings are important, as they indicate that a patient's insurance coverage can affect their access to ESAs. The findings also mean that physicians must account for a patient's insurance coverage in their prescribing decisions. While 10 health plans allowed physicians to prescribe any of the five ESAs as a first-line treatment, two plans allowed physicians to prescribe only a single ESA as the first-line treatment.

Health plans tend to more often apply coverage restrictions for some ESAs than for others. Plans most often applied coverage restrictions to methoxy polyethylene

glycol-epoetin beta and least often applied coverage restrictions to epoetin alfa-epbx—the only biosimilar in our five-drug review—and epoetin alfa (Procrit). Biosimilars are biological products that are highly similar (but not biologically identical) to, and have been determined to be clinically equivalent (in terms of safety and efficacy) to, a reference product.²⁰ Congress created the abbreviated licensure pathway for biosimilars with the intention of increasing competition, hence reducing health care costs.^{21,22} Although potential savings from biosimilar competition have been estimated to reach billions of dollars,^{23,24} biosimilar adoption has been slower in the United States than in other countries.²⁵ It is, therefore, noteworthy that plans least often restricted coverage of epoetin alfa-epbx (13 of the 14 plans covered epoetin alfa-epbx with no restrictions). For biosimilars to achieve the goal of reducing health care

FIGURE 4 Evidence Health Plans Cited in Their Coverage Policies for Erythropoiesis-Stimulating Agents for Patients with Anemia Due to Chronic Kidney Disease (N=62 Unique Studies)

costs, health care payers must make biosimilars available to physicians and patients. Further research must be conducted to determine if health plans have responded to the introduction of other biosimilars in a similar way as to plans covered epoetin alfa-epbx in this study or whether we have identified an unusual example of effective biosimilar competition in the United States.

The coverage differences we identified are consistent with findings for other diseases.^{9,10} While there are possible explanations, reasons for the variation are unclear. First, coverage differences may reflect different contracting arrangements that plans have with product manufacturers. Second, plans have different financial resources, and some plans may offer more generous coverage to attract enrollees. Third, plans may use different criteria when formulating their policies. For instance, we found that only two health plans in our sample reported reviewing health technology assessments.

We found substantial variation in the evidence that health plans cited in their coverage policies. One explanation for the variation could be that some plans tend to perform their own independent assessment of the evidence, while

others rely on clinical society recommendations. Indeed, we found that while half or more of the evidence cited by five health plans consisted of RCTs, half or more of the evidence cited by four health plans consisted of clinical or treatment guidelines. Another potential reason for the variation is that some plans report the evidence they review when formulating their coverage policies more thoroughly than other plans. Lastly, plan officials may prefer different types of evidence to inform their policies. For example, we found that only a single health plan cited any RWE.

Greater transparency with respect to the evidence health plans use for decision making would be beneficial to various stakeholders. For physicians and patients, transparency would help to convey the reasoning underpinning the level of access to certain treatments. Greater clarity would also aid product manufacturers in their design of clinical development programs so that manufacturers might generate evidence required for health plan decision making.

LIMITATIONS

Our study has a number of limitations. First, our findings may not generalize to commercial health plans not included

here or to public health care payers. More specifically, our findings may not generalize to Medicare, which covers a large proportion of patients with CKD.⁵ Second, we do not account for how often health plans may reverse coverage denials. Third, we did not account for patient cost sharing and other formulary management tools (eg, quantity limits). Fourth, we do not account for other types of citations that health plans included in their coverage policies, including—but not limited to—editorials and textbooks. Fifth, it is unclear whether plans cited all the evidence they reviewed when formulating their coverage policies. Finally, we do not know what types of evidence plans find most relevant and how plans weigh different types of evidence in decision making.

Conclusions

We identified substantial variation in how US commercial health plans cover ESAs for anemia due to CKD, suggesting that patients enrolled in different health plans may have unequal access to these drugs. Health plans varied with respect to the amount and types of clinical evidence they reported reviewing in support of their policies.

DISCLOSURES

This study was funded by Otsuka Pharmaceutical Development and Commercialization. Sanon, Redmond, and Mogahadam are employed by Otsuka Pharmaceutical. Michalopoulos was employed by Otsuka Pharmaceutical at the time of this study. Margaretos, Panzer, and Chambers are employed by Tufts Medical Center, Institute for Clinical Research and Health Policy Studies, Center for the Evaluation of Value and Risk in Health. Lai was with Tufts Medical Center, Institute for Clinical Research and Health Policy Studies, Center for the Evaluation of Value and Risk in Health at the time of this study.

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