Study of popular anemia drug supports new guidelines for its use in dialysis patients

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A new study helps dispel mounting confusion over the safety of blockbuster anemia drugs — erythropoiesis-stimulating agents — for people with kidney disease requiring dialysis, as federal regulators prepare to decide whether to impose additional restrictions on their use.

ESAs are the most expensive drugs reimbursed by Medicare in patients requiring long-term dialysis, costing the agency nearly $2 billion annually.

The new study, to be published March 3 in the Journal of the American Medical Association, zeroes in on which treatment practices for the anemia of patients on dialysis for severe kidney disease might be beneficial and which are potentially harmful. The finding: More-aggressive ESA treatment practices among the most-anemic patients were associated with better outcomes; by contrast, aggressive treatment of patients with milder red-blood-cell deficiencies was associated with increased mortality.

The study's senior author, Wolfgang Winkelmayer, MD, ScD, associate professor of medicine at the Stanford University School of Medicine, conducted the research while on the faculty at Harvard Medical School.

The findings are certainly timely. Over the next four months, the U.S. Food and Drug Administration and the Centers for Medicare and Medicaid Services are set to review the use of ESAs in treating anemia in patients with chronic kidney disease. "Eliminating coverage or

severely restricting marketability of ESAs might mean pouring out the baby with the bath water," said Winkelmayer, "We give glimpses that show that such extreme action might not be warranted."

Anemia, a common complication of kidney disease, is the result of too few healthy red blood cells, leading to a decrease in the blood's ability to carry oxygen. There are currently three ESA products used in the United States to treat it: darbepoetin alfa, marketed by the biotech company Amgen as Aranesp, and epoetin alfa, marketed, respectively, by Amgen as Epogen and by Johnson & Johnson as Procrit.

While ESAs were approved for use for the treatment of anemia in 1989, questions have emerged in recent years over their safety for different subsets of patients.

Cancer patients with anemia often initially respond well to ESAs, but studies have shown that ultimately the drugs can cause tumors to grow faster and shorten patients' lives. As a result, on Feb. 16, the FDA unveiled a plan requiring physicians to complete special training before prescribing ESAs for cancer patients.

The new study looks at the safety of ESAs for a different patient population, comprising another major group of the drugs' users: people with severe kidney failure requiring long-term dialysis treatment — also known as end-stage renal disease. The condition affects about 530,000 people in the United States and roughly 350,000 of them are on long-term dialysis, meaning they rely on a dialysis machine to do the work of their kidneys, typically undergoing three- to four-hour treatments three times a week.

"Clearly, recent trials have revealed potentially serious safety issues for ESAs in end-stage renal failure patients," said Winkelmayer. "But until our study, no one has been able to link the findings from selected trial

populations of a few hundred or thousand patients to the larger population of typical patients undergoing maintenance dialysis."

In the decades since the first of these drugs gained FDA approval, researchers have tried to assess their impact on patients' risk of serious, potentially fatal cardiovascular events, like a stroke or heart attack. Researchers had observed that patients receiving higher levels of ESAs had increased risk of these negative outcomes, but proof of a cause-and-effect relationship eluded them.

"Researchers have looked at this a hundred different ways," said Winkelmayer. "It's occupied a generation of drug safety researchers. Unfortunately, patients requiring lower ESA doses for the management of their anemia are inherently different from patients requiring larger doses — making it almost impossible to discern whether the inferior outcomes experienced by patients receiving high ESA doses were attributable to the medication itself or to differences in patient characteristics, which were usually poorly described in the available datasets."

Winkelmayer's collaborators were lead author M. Alan Brookhart, PhD, now at the University of North Carolina; three other former Harvard colleagues; and a scientist at Amgen, which provided funding to support the research.

Winkelmayer and his co-authors took advantage of a natural experiment created by the use of varying treatment protocols at dialysis centers throughout the United States. The team analyzed data on patients' treatment with ESAs and intravenous iron at about 4,500 U.S. dialysis units, creating a unit-specific anemia management profile for each calendar year between Jan. 1, 1999, and Aug. 31, 2006. Then, the researchers determined the one-year mortality risk associated with the various management protocols.

"What we found was that the facilities treating anemia most aggressively with an ESA among people who were severely anemic, with a hematocrit of less than 30 percent, had better outcomes," said Winkelmayer.

"But using ESAs most aggressively among those patients whose anemia was relatively mild, having a relatively high hematocrit of 36 percent and higher, was associated with higher mortality," he added.

The hematocrit is the proportion of blood that consists of red blood cells; the lower the hematocrit, the more anemic the patient.

They found that patients treated in facilities that offered the most aggressive treatment for people with hematocrits above 36 had an 11 percent higher risk of mortality compared with those treated in facilities that had the least aggressive treatment.

More- or less-aggressive ESA treatment among patients with intermediate hematocrits had no impact one way or the other, Winkelmayer said.

"Findings for iron treatment followed a similar pattern," Winkelmayer said. "Facilities with greater use of intravenous iron at low hematocrit had better outcomes, whereas more-aggressive iron use among patients with relatively higher hematocrit was associated with increased mortality."

The finding could influence regulatory agencies' decisions about reimbursement or labeling for ESAs. On March 24, the Centers for Medicare and Medicaid Services are convening a Medicare Evidence Development and Coverage Advisory Committee to review the available evidence on the use of ESAs to manage anemia in patients who have chronic kidney disease, and the FDA has already indicated that it will follow suit later this spring.

Aside from their use as anemia treatments, ESAs also have a history of use as a blood doping agent in endurance sports such as cycling and distance running.

Winkelmayer noted that more information is needed on ESAs' effects over a longer time period, as this study was based on new dialysis patients with follow-up limited to one year. Further studies are also needed in patients with chronic kidney disease who do not yet require dialysis as well as in patients receiving peritoneal dialysis, a less common form of dialysis. This paper looked only at patients undergoing hemodialysis, the most prevalent form of dialysis.

"I'm not sure whether we can appreciate a full picture yet," Winkelmayer said. "A very careful and differentiated look at the existing evidence will be required."

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