Racism a Public Health Crisis

Continued from page 9

other public health interventions and more concrete structures that would allow for addressing racial disparities and health," she added. "So, I think, from a social and public health standpoint, these types of statements do have a lot of impact." ■

References

1. Franklin County Public Health. Franklin County Board of Health Declares Racism a Public Health Crisis. May 13, 2020. https://myfcph.org/franklin-county-board-of-health-declares-racism-a-public-health-crisis/
2. Tyson P, et al., sponsors. Resolution Declaring Racism a Public Health Crisis in Columbus (The City of Columbus City Council). 2021; 0095X-2020. https://www.columbus.gov/racismresolution/
3. US Department of Health and Human Services, Office of Minority Health. Diabetes and African Americans. December 19, 2019. https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=4&lvlid=18
4. Office of Disease Prevention and Health Promotion. Social Determinants of Health. October 8, 2020. https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-of-health
5. Artiga S, et al. Racial Disparities in COVID-19: Key Findings from Available Data and Analysis (Kaiser Family Foundation). August 17, 2020. https://www.kff.org/racial-equity-and-health-policy/issue-brief/racial-disparities-covid-19-key-findings-available-data-analysis/
6. Hoffman KM, et al. Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. *Proc Natl Acad Sci USA* 2016; 113:4296–4301. doi: 10.1073/pnas.1516047113
7. Associated Press. Black doctor dies of COVID after racist treatment complaints. December 25, 2020. https://apnews.com/article/race-and-ethnicity-indianapolis-media-social-media-coronavirus-pandemic-e9332a29f-d5a202664c4eae0989add10
8. Chambers S. North Carolina Healthcare Association Issues Statement on Racism as a Public Health Crisis (North Carolina Healthcare Association). November 17, 2020. https://www.ncha.org/2020/11/north-carolina-health-care-association-issues-statement-on-racism-as-a-public-health-crisis/

Did Roxadustat's Results Change from Blockbuster to Lackluster?

By Eric Seaborg

The news from FibroGen that roxadustat's safety profile is not as positive as it had previously reported considerably dampened enthusiasm for a drug that some had been awaiting with anticipation, according to several nephrologists.

Roxadustat is part of a new class of drugs, called hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs), for treating chronic kidney disease (CKD)-related anemia. HIF-PHIs have been touted as possibly safer replacements for the erythropoiesis-stimulating agents (ESAs) that have been mainstays for more than 30 years but are associated with cardiovascular risks.

The US Food and Drug Administration (FDA) surprised FibroGen and AstraZeneca, with whom the company has been collaborating in the drug's development, by asking for a meeting of its Cardiovascular and Renal Drugs Advisory Committee to review the company's new drug application for roxadustat. In turn, FibroGen stunned many observers when CEO Enrique Conterno announced in a press release on April 6, 2021: "As members of the senior management were preparing for the upcoming FDA Advisory Committee meeting, we became aware that the primary cardiovascular safety analyses included post-hoc changes to the stratification factors. We promptly decided to clarify this issue with the FDA and communicate with the scientific and investment communities."

The press release revealed that the company's previous evaluations had analyzed the drug's safety using "post-hoc stratification factors" rather than the proper "pre-specified stratification factors." FibroGen did not specify what the post-hoc changes in the stratification factors were, but the net effect was to remove roxadustat's evident safety advantage compared with the drugs it would presumably replace.

Previous publications had indicated that clinical trials had found roxadustat's safety to be superior to an ESA in incident dialysis patients, comparable to placebo in nondialysis patients, and comparable to an ESA in dialysis patients.

"All the superiority claims have now gone away … and the noninferiority claims, while not dramatically different, are a little bit worse," said Daniel W. Coyne, MD, professor of medicine at Washington University in St. Louis. He has been a site investigator for both roxadustat and daprodustat, another drug in the HIF-PHI class, and has been co-author on publications and abstracts for roxadustat. In a conflict-of-interest statement for the March 2021 *KN* article, "Novel Anemia Treatment: HIF-PH Inhibitors," Coyne stated he has been a consultant to the manufacturer of all three HIF-PHIs.

Losing their advantage

The lack of a safety advantage deals a significant blow to the drug's value as a replacement for ESAs, because it is the cardiovascular risks of ESAs that limit their use to patients on dialysis.

"I think this changes everything," Coyne told *ASN Kidney News*. "This means that they don't have a distinct advantage over our present standard of care, ESAs. It shifts the balance of what the role of these drugs is."

"We have all had safety concerns about the EPO [erythropoietin] analogs," said Katie Kwon, MD, FASN, a nephrologist in private practice at Lake Michigan Nephrology in St. Joseph, MI. "My thought process was, if this were safer than EPO and gave the same control of anemia, I would switch, for sure. I would not be excited to switch if it were equivalent, because I don't know how much it is going to cost. And it is a big deal to change up your protocols and learn the ins and outs of dosing a new drug. There is a significant investment of time and resources in that switch."

The NephJC podcast, Freely Filtered, devoted an edition to "The Roxadustat Statistical Shenanigans." One of the hosts, Swapnil Hiremath, MD, MPH, a staff nephrologist at Ottawa Hospital and associate professor of medicine at the University of Ottawa in Canada, said the original safety superiority numbers were "such a dramatic result [that] it was going to be a no-brainer that these drugs should be used. I was keen on using them. I am looking at them now and saying, 'I'm not sure I'll switch.' Now, I am [seeing them as] one more ESA."

Questions of credibility

In addition to the change in perception of the drug, the "statistical shenanigans" are leading to a large loss in credibility for FibroGen. Despite his involvement in research for the company, Coyne received no notice that it was about to issue what the company described as a "clarification." Coyne first heard about the press release while presenting at a National Kidney Foundation Spring Clinical Meetings symposium on the HIF-PHI class—when he received a question from the audience. "This deeply damages the reputation of FibroGen going forward," Coyne said. "I feel very misled, and I don't think there is any excuse for this. I don't know how this could happen accidentally."

"I am really shocked that a mistake of this magnitude was made," Kwon said. "If these drugs ultimately are approved, my evidence threshold for when I am going to feel comfortable using them is going to be quite a bit higher."

Roxadustat has been approved for use in Japan and China and had been considered to have the inside track to be the first in the class to gain FDA approval. The consensus of the speakers on the Freely Filtered podcast was that the drug had demonstrated efficacy, so they expected the FDA to approve it.

FibroGen said the revelation should not affect its application to the FDA, because "there is no change to the underlying data, or to the efficacy analyses from the Phase 3 program." That left observers all the more mystified about the reason for the presumed data manipulation, considering that the FDA would receive the raw data and make its own analysis and conclusions. Hiremath said the company had demonstrated "noninferiority…. That was good enough…. The FDA see[s] the raw data."

Still, the nephrology community will be watching the literature carefully for updates. At least one roxadustat paper "will be retracted and replaced with a corrected version," *KI Reports* Executive Editor Radha McLean said in an email to *ASN Kidney News*. "The authors are in the process of making the corrections" to the paper, "Pooled analysis of roxadustat for anemia in patients with kidney failure incident to dialysis" (1), which was published online on December 24, 2020. ASN retracted Abstract FR-OR131 [Pooled Efficacy and Cardiovascular (CV) Analyses of Roxadustat in the Treatment of Anemia in CKD Patients on and Not on Dialysis, submitted to ASN Kidney Week in 2019] (2). A statement on the ASN website reads: "This retraction is based on close review according to ASN meeting and peer-review policies, and this review identified significant concerns regarding the accuracy of the data presented at ASN Kidney Week 2019."

In two recent trials published in the *New England Journal of Medicine* (3, 4), the HIF-PHI vadadustat showed inferior outcomes in respect to cardiovascular events in CKD patients and noninferior outcomes in dialysis patients.

Coyne noted that the change in roxadustat's status could raise the stakes for the upcoming release of clinical trial results of the HIF-PHI daprodustat, given that the recent safety results from the other drug in the class, vadadustat, "looked inferior in the nondialysis patients vs. ESAs." Daprodustat trials "may turn out to be the tie-breaker" on the safety of this new class of drugs, he said. ■

References

1. Provenzano R, et al. Pooled analysis of roxadustat for anemia in patients with kidney failure incident to dialysis. *Kidney Int Rep* 2020; 6:613–623. doi: 10.1016/j.ekir.2020.12.018
2. Provenzano R, et al. Pooled efficacy and cardiovascular (CV) analyses of roxadustat in the treatment of anemia in CKD patients on and not on dialysis. ASN Kidney Week. November 8, 2019; FR-OR131. https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3275139
3. Eckardt K-U, et al. Safety and efficacy of vadadustat for anemia in patients undergoing dialysis. *N Engl J Med* 2021; 384:1601–1612. doi: 10.1056/NEJMoa2025956
4. Chertow GM, et al. Vadadustat in patients with anemia and non-dialysis-dependent CKD. *N Engl J Med* 2021; 384:1589–1600. doi: 10.1056/NEJMoa2035938