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Emerging Treatment for Anemia of CKD: HIF-PH Inhibitors

Announcer Open:
Welcome to CME on ReachMD. This activity titled Emerging Treatment for Anemia of CKD: HIF-PH Inhibitors is provided by Clinical Care Options, LLC and is supported by an educational grant from GlaxoSmithKline. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Wish:
Welcome to Medical Minute 3, Emerging Treatment for Anemia of CKD: HIF-PH Inhibitors. My name is Jay Wish, I'm Professor of Clinical Medicine at Indiana University and Chief Medical Officer for Out-Patient Dialysis at Indiana University Health in Indianapolis. Here you see my disclosures. Our learning objective for this session will be to summarize the efficacy and safety data for HIF-PH inhibitors compared with conventional treatment of anemia for CKD.

First question is, how many patients with CKD do you provide care for in a typical week? And you have 6 choices, please enter your vote. Our presurvey question is, in a randomized open-label phase 3 trial, which of the following best describes the primary outcome of daprodustat versus an injectable ESA in patients with CKD undergoing dialysis? You have 4 choices, please enter your vote.

An outline for our presentation is on this slide. We'll discuss the mechanisms of action of the HIF-PHIs, especially the role of the oxygen-sensing pathway and how the HIF-PHIs leverage this pathway to treat anemia and CKD. We'll explore the investigational evidence to date, including phase 3 efficacy compared with ESA, and adverse events including cardiovascular safety with some controversy and discussion of this issue, as well as the potential place for HIF-PHIs in the treatment of anemia chronic kidney disease.

HIF pathway was discovered by William Kaelin, Peter Ratcliffe, and Greg Semenza, who were awarded the 2019 Nobel Prize in Medicine and Physiology for this discovery. HIF, or Hypoxia-Inducible Factor, is a family of oxygen-sensitive proteins that regulate the cells transcriptional response to hypoxia. So, in other words, this is how our body, and the body of other animals, respond to a decrease in oxygen delivery to the tissues. It turns out that it's a central regulator of erythropoiesis and response to hypoxia, including the production of erythropoietin, or EPO, and indirect suppression of hepcidin by this promotion of erythropoiesis, augmentation of enteric iron absorption and transport and mobilization of endogenous iron stores through the erythroid marrow to make more iron available as a building block for hemoglobin synthesis.

HIF is a heterodimer consisting of 2 subunits, an alpha subunit and a beta subunit. The alpha subunit is continuously produced and degraded if oxygen is available to the tissue. The beta subunit is continuously present. The mechanism for the regulation of the alpha subunit is shown in this slide. Each alpha has 2 proline residues, which can be hydroxylated by HIF-PH, HIF prolyl hydroxylase, in the presence of oxygen. The other necessary co-factors for this reaction include iron and 2-oxygluterate, also known as a-ketoglutarate. If oxygen is present and these other cofactors are also available, the 2 proline residues are hydroxylated, as you see with the OH, and this changes the configuration of the molecule, so it is recognized and undergoes degradation by Von Hippel-Lindau protein and ubiquitin.

If low oxygen tension is present, or a chemical compound is used that interferes with the interaction with 2-oxygluterate, which is how these HIF prolyl hydroxylase inhibitors work, then the proline residues on the HIF alpha are not hydroxylated and the HIF alpha basically escapes degradation, migrates to the nucleus where it dimerizes with HIF beta, which is continuously present. This HIF heterodimer

then allows for the transcription of a variety of genes known as hypoxia-responsive elements, or HRE. And these genes include not only the erythropoietin gene, but also the EPO receptor, divalent metal transporter 1 and duodenal cytochrome B, which improve enteric absorption of iron, transferrin, which carries iron through the body to the erythroid marrow. There's also an up-regulation of the transferrin receptor, as well as ceruloplasmin, which helps convert divalent iron to trivalent iron for carriage by transferrin.

There is a family of compounds that have been developed to interfere with the degradation of HIF alpha, and these have been called HIF prolyl hydroxylase inhibitors, HIF-PHIs, or HIF stabilizers. The advantage of these compounds over conventional therapy for renal anemia, which basically includes ESAs, which have to be administered perineurally, is that these are all small molecules that can be administered orally. They are reversible. So, the HIF transcriptional activity returns to baseline between the doses, and this minimizes any off-target effects of HIF stabilization that might react with other undesirable outcomes.

There are 3 agents in this class that are currently undergoing development in the United States, roxadustat, vadadustat, and daprodustat. On the right-hand side of this slide, you can see the chemical formulas, but the main thing that I want to point out with – to you is that the right portion of each of these formulas is similar, and this is basically the analogue of 2-oxygluterate which displaces this essential cofactor from the HIF prolyl hydroxylate complex and renders it ineffective in degrading HIF alpha.

You can see in this slide the pharmacologic profiles of these 3 HIF stabilizers that are underdeveloped in the United States. The half-life is different so that the dosing schedule between these agents is also different.

Roxadustat is administered 3 times weekly. Vadadustat and daprodustat were originally considered once daily treatment, but phase 2 studies with vadadustat indicated that it can be administered 3 times weekly. And phase 3 studies with daprodustat indicated that it can be affectively administered 3 times weekly.

You can see the plasma EPO levels for each of these agents, which is in the 30 to 100 or so range. And this is significantly less than the plasma EPO levels that are achieved following a single injection of erythropoietin alpha. The relative activity of each of these agents for the prolyl hydroxylase domain enzymes, and there are 3 of them – PHD 1, 2 and 3, are seen on the bottom line of this table, and they are somewhat different between the 2 agents. Whether this has any clinical significance remains to be seen.

So, roxadustat is the first-in-class HIF stabilizer. It had a large global phase 3 clinical trial of about 4,000 patients, the non-dialysis, and another 4,000 patients undergoing dialysis. Its new drug application was rejected by the FDA in August 2011 due to safety concerns, particularly regarding access thrombosis and venous thromboembolism. However, the new drug application was approved by the European Medicines Agency, which is like the FDA for the European Union, later in August of 2021 and roxadustat has also been previously approved in China, Japan, Chille and South Korea, and was subsequently approved in the United Kingdom.

Vadadustat has been approved in Japan. Its new drug application was submitted to the FDA in June of 2021 and rejected in March of 2022. Their global phase 3 clinical trials were presented at ASN 2020 Kidney Week and published subsequently in the *New England Journal* on April 29, 2021. There are 2 major studies, the INNO2VATE studies in dialysis dependent patients, both insulin and prevalent, and the PROTECT studies in the non-dialysis patients including both ESA naïve and previously ESA treated patients. And darbepoetin was the comparator in both of those trials.

Daprodustat has also been approved in Japan. There are 5 global phase 3 studies, which you can see here. For incident dialysis patients given 3 times weekly. In prevalent dialysis patients, an NHQ study, which looks specifically at quality of life versus placebo. The DIALYSIS study which included about 3,000 prevalent dialysis patients, and the non-dialysis, or ND, study which included about 4,000 non-dialysis patients. The results from the D and ND studies were reported at ASN 2021 Kidney Week and published simultaneously in the *New England Journal* ahead of print in November 2021. And the FDA Cardiorenal Drug Advisory Committee just a short time ago, on October 26, 2022, voted 13 to 3 for its approval in dialysis dependent patients and 11 to 5 against approval in non-dialysis patients. These recommendations of the Cardiorenal Panel are not binding, and the ultimate disposition of the new drug application for daprodustat by the FDA has yet to occur.

Now, this slide summarizes the mean hemoglobin changes from baseline in non-dialysis patients for the large phase 3 clinical trials of the HIF stabilizers vadadustat, roxadustat, and daprodustat.

On the left-hand side of this side, you can see the placebo-controlled trials involving roxadustat versus placebo, and almost all of them indicated a about 2 g/dL increase in hemoglobin versus placebo over the course of the study.

On the right-hand side of the slide, you can see the studies that were done with a darbepoetin comparator, the DOLAMITES study for roxadustat, the PRO2TECT Correction and Conversion study, Correction being the ESA-naïve, and Conversion study being ESA-previously treated, and the ASCEND-ND patients in the daprodustat. And you see very easily by the length of the bars that the efficacy was pretty much non-distinguishable to that of darbepoetin.

In this slide you can see the mean hemoglobin changes from baseline in dialysis patients among the three HIF-PHIs that we've mentioned. For the pooled analysis incident and prevalent patients using roxadustat, vadadustat, and daprodustat, the differences between the hemoglobin achieved and that of daprodustat were felt to be clinically insignificant and any small differences were attributed to the dosing protocols for the HIF-PHI and not to any inherent differences in efficacy, either between the agents or compared to the control daprodustat – control darbepoetin.

Here you see the hemoglobin and noninferior margins that were used during these main randomized controlled trials of the HIF-PHIs roxadustat, vadadustat, and daprodustat had a hemoglobin target that depended upon whether the study was conducted in the U.S. or outside the U.S. In the U.S. the hemoglobin target was generally 10 to 11, and outside the U.S it was generally 10 to 12. The noninferior margin for MACE, as you can see, was 1.3 for roxadustat, 1.25 for vadadustat in the U.S. and 1.3 outside the U.S, and for daprodustat it was 1.2, and subsequently changed to 1.25. And again, on the right side of the slide you can see the main competitor. For non-dialysis patients, again the hemoglobin target range depended upon whether it was a U.S. or non-U.S. study and the noninferior margin for MACE was similar for each agent as to what occurred in the dialysis study, a little higher for roxadustat, 1.25 for vadadustat in the United States, and 1.25 for daprodustat. I should point out the noninferior margin of 1.3 of roxadustat was not agreed with by the sponsor in the FDA prior to the design of the study whereas the other agents, vadadustat and daprodustat, their upper margin of MACE noninferiority was in fact agreed upon with the agency.

So, what did the FDA decide regarding these agents? There were safety issues that as you already saw, led to the rejection by the FDA of roxadustat and vadadustat. For roxadustat in non-dialysis patients versus placebo, there was an increase incidence of thrombotic events including DVT and pulmonary embolus, increased seizures and increased infections. In roxadustat versus dialysis patients the MACE noninferiority margin of 1.30, as I said, was not prespecified by the FDA and that is in fact what the noninferiority margin was and the FDA prespecified a 1.25 margin for the other 2 agents, as you recall. There as increased incidence of DVT and vascular access thrombosis versus ESA for roxadustat in dialysis patients.

For vadadustat versus ESA, it did not achieve the prespecified MACE noninferiority upper bound of 1.25. There was an increased incidence of thrombotic events including DVT and pulmonary embolus, and there was suspicion of some drug-induced liver injury. There was mild increases in transaminases which resolved following discontinuation of the drug, but nonetheless the FDA was sufficiently concerned that this was one of the factors that led to it's failure to approve the drug. In dialysis patients versus ESA, the FDA claimed that there was increased vascular access thrombosis and drug-induced liver injury, but this is not supported very well by the published data.

The FDA Cardiorenal Drug Advisory Committee, which met regarding daprodustat in October of 2022. The drug met the specified MACE noninferiority upper bound confidence interval of 1.25. However, there was increased incidence of hospitalization for heart failure among patients with a previous history of heart failure, you can see the hazard ratio of 1.51. There was increased incidence of what were called serious esophageal and gastric erosions, you can see the hazard ration of 1.96. However, I should point out that this did not lead to any differences in the achieved hemoglobin levels or increases in transfusion rates among the daprodustat-treated patients versus ESA. There was also an increased incidence of acute kidney injury, 1.47, but this did not lead to any increase in the rate of decline of overall kidney function, or increased mortality, or need for dialysis.

For dialysis-dependent patient versus ESA, the major safety issues raised by the FDA, which however, did not interfere with the approval of the drug by the Cardiovascular Renal Committee, included the fact that it did meet the prespecified MACE noninferiority upper bound of 1.25. The hospitalization for heart failure here was 1.44 hazard ratio, but you can see the 95% confidence interval crossed 1 making it not statistically significant. And there was increased hazard ratio of 1.16, or serious esophageal and gastric erosions, but again, the 95% confidence interval crossed 1 making it of questionable statistical significance.

So, next question is, in a randomized open-label phase 3 trial, which of the following best describes the primary outcome of daprodustat versus an injectable ESA in patients with CKD undergoing dialysis? You have 4 options, please enter your vote.

So, to summarize the cardiovascular safety of HIF stabilizers in non-dialysis dependent CKD patients, as you saw, there were more thrombotic events with roxadustat versus placebo. But this may have been related to the duration of exposure as the placebo-treated patients dropped out of the study much earlier than those receiving roxadustat because not having their anemia treated, they were much more symptomatic and were in fact more likely to start on dialysis because of many of these symptoms. Vadadustat as you saw failed to demonstrate MACE noninferiority to ESA. It crossed the prespecified upper bound of the confidence interval for MACE of 1.25.

And daprodustat did demonstrate MACE noninferiority to ESA in the primary intention to treat analysis, but not in the supportive on-treatment analysis.

In dialysis dependent patients, roxadustat demonstrated a higher rate of thrombotic events including vascular access thrombosis versus ESA, which was the main reason why the FDA rejected the dialysis indication for this drug. Vadadustat also demonstrated MACE noninferiority but as I mentioned, the FDA claimed that there was a higher rate of thrombotic events, which was not supported by published data. And finally, daprodustat did demonstrate MACE noninferiority to ESA in the primary intention to treat analysis, and also in the secondary on-treatment analysis, which is probably the reason why the CRDAC voted positively to recommend approval of the drug in the dialysis setting.

So, the potential place for HIF-PHIs in therapy. They are administered orally, so for patients who are currently receiving injectable ESAs, especially non-dialysis patients, this may be a more patient-friendly way to give a treatment for anemia since the patient can take the oral drug at home rather than having to come to a healthcare provider to receive erythropoietin stimulating agent injections. HIF-PHIs have been to have beneficial effects on iron metabolism, as I showed you part of their mechanism of action is to increase the transcription of a variety of iron transport proteins both in the gastrointestinal tract and in the reticuloendothelial system increasing the delivery of iron to the erythroid marrow, which may make them more affective than ESAs, or not iron replete. However, the decrease in iron requirements among dialysis dependent patients receiving daprodustat and roxadustat where it was actually assessed was not felt to be of significant clinical benefit.

For non-dialysis CKD patients with severe anemia who are undertreated with currently, as you may be aware, they are more likely to have received a transfusion than an ESA during the 2 years prior to dialysis initiation. Again, the barriers to ESA treatment leaves many of these patients inadequately served as far as raising their hemoglobin and then, when the hemoglobin gets low enough and the patient has become symptomatic, they end up getting transfused. We do not favor transfusion as a treatment for CKD of anemia because transfusions can lead to allosensitization, which decreases the potential pool of transplant donors for that patient, and also increases the likelihood of rejection of the transplanted organ.

Also, the HIF-PHIs may offer a more convenient anemia treatment than ESAs in the expanding home dialysis population. Again, the major advantage of HIF-PHIs being their oral route of administration so the patients can take them at home rather than having to travel to their dialysis center to receive the injectable ESA, and as you may be aware, the home dialysis population is expanding because of a variety of federal incentives to keep more patients at home to increase their quality of life and to decrease the overall cost of the end-stage renal disease program.

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