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Challenging Cases in CKD Anemia: The Kidneys and Heart as Linked Parts

Announcer:
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Dr. Singh:
Hello, and welcome to our program, Challenging Cases in CKD Anemia: The Kidneys and Heart as Linked Parts. My name is Dr. Ajay Singh. I'm a nephrologist at the Brigham and Women's Hospital and Faculty at Harvard Medical School. Joining me today is my colleague Dr. Kirsten Johansen, Chief of Nephrology at Hennepin and a Professor of Medicine at the University of Minnesota.

Here are our disclosures.

Here are the learning objectives: clarify the disease burden imposed by untreated or undertreated anemia in patients with chronic kidney disease, CKD, including in racially diverse populations. Two, correlate the pathophysiology of anemia and CKD with viable therapeutic targets. And three, identify appropriate candidates for emerging CKD related anemia treatments among patients on or not on dialysis based on efficacy and safety data from recent clinical trials.

Let's start the conversation with an overview of CKD anemia.

Dr. Johansen:
Thank you, Dr. Singh. Let's first just talk about the prevalence of anemia, and even before we get to the prevalence of anemia, the prevalence of chronic kidney disease. Over 15% of adults in the U.S. are estimated to have chronic kidney disease. The prevalence is a little higher in women than in men when we look in the general population, and of course, much more prevalent among older individuals. But up to 90% are undiagnosed, and even about 40% of those with severe chronic kidney disease are undiagnosed.

When it comes to the prevalence of anemia itself, anemia is much more likely to occur in patients with chronic kidney disease, about two and a half times as likely. This slide is showing a retrospective analysis of hemoglobin levels in patients with chronic kidney disease, about 22,000 people. And what you can see is that almost a quarter of patients with non-dialysis dependent chronic kidney diseases, overall stages 3a to 5, had anemia defined by a hemoglobin less than 10. But the prevalence increased as the CKD stage increased, as well, from 18.2%, down at 3a all the way up to 72.8% at stage 5. So the majority of patients with advanced CKD have anemia.

And in terms of the consequences of that anemia, the first one we think about is symptoms. Patients experience a lot of symptoms with anemia. They tend to shake out in a couple of domains, in particular, weakness, tiredness, low energy, or you might call that fatigue, these first ones. And then the second would be shortness of breath during rest or activity. And then the last is sometimes a cognitive domain with difficulty remembering things, etcetera. And then physical and emotional impacts can include difficulty standing for long periods of time, difficulty sleeping, needing breaks and naps, and feeling distressed and burdensome.

In terms of the impact of CKD-related anemia on long-term health outcomes, we can think of this in a number of things. We talked a little bit already about the reduced health-related quality of life, but there's also a higher risk of volume overload and heart failure. And there's also a higher risk of hospitalization and mortality, which I think is really important given the already high rates of that among patients with chronic kidney disease, just to recognize that it's higher yet among those who have anemia.

This slide is just to highlight some of the associations between the risks of CKD and CKD anemia, and how those may fall disproportionately among members of certain race ethnicities group. First of all, CKD risk is much higher among black, Hispanic, and Native American individuals, compared with members of other race ethnicity groups in the U.S. There's a much higher rate of kidney disease, probably in part because of higher rates of diabetes and hypertension, and then also a higher risk of kidney failure. Incident dialysis is almost four times higher among black than white individuals and also 1.3 times as high among Hispanic, and 1.2 times as high among Native Americans, as well. And in addition to having a higher burden of chronic kidney disease, they're less likely to receive optimal treatment of their kidney disease, in particular, transplantation and home dialysis.

And those treatment disparities are most pronounced among our youngest patients. For example, black patients with CKD are about two and a half to three and a half times more likely to have CKD-related anemia compared with others. So higher burden of CKD itself, and then a higher burden of anemia with CKD.

So Dr. Singh, how do you think our understanding of the pathophysiology of anemia and chronic kidney disease has changed over the past few years,

Dr. Singh:
Probably the most substantial changes have been our understanding and insights into the regulation of systemic iron homeostasis. Two important discoveries, I think, inform this knowledge. The first is the discovery of the central role of hepcidin, which is, as you know, and we'll discuss later, is a key liver synthesis protein. Hepcidin has a really substantial effect on the – on ___ pathophysiology and on iron mobilization.

And then the second thing I think, is the discovery and the role of erythroferrone which is a major erythroid regulator of hepcidin. Erythroferrone is produced by erythroblasts and inhibits the production of hepcidin in the liver. So together hepcidin synthesized by the by the liver, and erythroferrone primarily synthesized by erythroblasts regulate iron absorption and iron mobilization.

Interestingly, erythroferrone is stimulated by red cell production, in essence, and its activity is regulated by erythropoietin binding to its receptor and then activating the JAK2-STAT5 signaling pathway. So this access, I think, and its his discovery has been very, very important.

Dr. Johansen:
I agree. I remember when I was training, hearing about inflammation and how inflammation led to anemia of chronic disease, but no one really understood the mechanism fully back then, I think. And we may not understand it fully now, but that role of hepcidin that you were talking about is just so interesting, and so critical. And the idea that ferroportin is necessary is the thing that sort of turns on iron availability from absorption in the duodenum, to release from the liver, and macrophages and that hepcidin come in and turn that off so that iron isn't available. And that that whole idea of functional iron deficiency that I feel like we didn't understand, now just seems like it makes so much more sense.

Dr. Singh:
Right. And you know, it's you just alluded to, the fact that hepcidin is also excreted by the kidney. So as a kidney function worsens, hepcidin levels increase, hepcidin inhibits essentially mobilization of iron and iron movement through the GI tract, and it means that the absorption of oral iron in patients with progressive kidney disease, becomes progressively impaired. That was a clinical observation we all struggled to understand several years back which now has become clearer. The other thing that -

Dr. Johansen:
Right. You mean the reason why people with chronic kidney disease have so much iron deficiency actually, frank iron deficiency?

Dr. Singh:
Right.

Dr. Johansen:
Right. Exactly.

Dr. Singh:
Absolutely. And then the other point I'm trying to make is, with, you know, increasing hepcidin levels, you have to ask the question, well, what's causing that? One was we didn't know that erythroferrone on this newly discovered protein that's sort of synthesized by

erythroblasts even existed a few years ago. That's number one. And number two, that hepcidin can be - or synthesis can be increased via the liver and in following inflammatory stimuli and heightened levels of cytokines like IL-6 and IL-1. All of this stuff was relatively unknown. And so I think it's really pretty exciting that we've now got insights into this and sort of explain some of the clinical observations we struggled to explain years ago.

Dr. Johansen:
I'm going to talk just a little about the pathophysiology of anemia in chronic kidney disease. It's really multifactorial, and I think we've always known that, but there's possibly even a little bit more understanding of that right now that blood loss directly occurs in chronic kidney disease. And then inflammation can occur, which can increase hepcidin levels as we were talking about before, which then in turn can lead to iron deficiency. And then uremic toxins can shorten red blood cell lifespan. And then, of course, we all have known for a long time that with kidney failure, there's decreased production of erythropoietin. And so all of these things combined together to really cause and exacerbate anemia as chronic kidney disease continues to progress.

So in terms of how we take that pathophysiology, and translate it into treatment, we have really three main pillars of treatment right now. The first is iron administration to address that iron deficiency. And we'll talk a little bit more about that later about how we do that and what the limitations are there. Second, we can administer now erythropoietin-stimulating agents to address the decreased EPO production. And then third, less desirable, but still effective is transfusion to replace red blood cells.

Let's talk a little bit about considerations and limitations of the current treatments. So ESAs, as we call them, erythropoietin-stimulating agents, stimulate red cell production and raise hemoglobin, but they're associated with cardiovascular risk at higher doses or at higher hemoglobin targets. As a result, the FDA recommends that we use the lowest dose needed to reduce red blood cell transfusion requirements, rather than even a specific hemoglobin target. And about 10% of patients show hypo-responsiveness or resistance to ESAs, even at high doses.

And of course, other considerations are just the practical ones. They require parental oral administration, they require cold storage, they are quite expensive, and they're difficult for patients to receive and for clinic staff to administer.

In terms of iron supplementation, it also often raises hemoglobin, especially in conjunction with ESAs. But oral administration is associated with poor absorption and also causes a lot of Gi side effects that sometimes limit the adherence.

So I.V. administration is often needed. And it's much better tolerated. You can give larger doses, and you can replete iron much more quickly, but it has the potential for iron overload, and may worsen CKD-associated inflammation and has a small risk of anaphylactic reactions. But again, important consideration is just the practical. It requires I.V. access, and it requires a transfusion or an infusion clinic, it can't be given just in a usual regular clinic. So there's usually a delay and some difficulty in arranging it. So these therapies are effective, but they do have their limitations.

So perhaps as a result of all of the things that I've been talking about, the potential side effects, potential safety concerns, and the practical difficulties of receiving some of these treatments, there are a lot of shortcomings in how we're doing and how we're treating patients. There was a prospective cross-sectional analysis of data from nephrology clinics in four countries, including the U.S., almost 7,000 patients with stage 3 to 5 chronic kidney disease. And they found that hemoglobin was measured less often than recommended by guidelines. And then anemia was rarely treated to guideline-recommended targets above 10 grams per deciliter.

Another study that was in U.S. that was a retrospective analysis based on claims data, almost 23,000 patients with CKD stages 3 to 5 with anemia, they found that an extremely low percentage of patients received I.V. iron, less than 1%, and only about 2% were treated with erythropoietin-stimulating agents.

So we are just not treating patients even when they have anemia at the current time. And that has an impact. That has a potential impact on patients. When you think about, as we discussed earlier, that there's a higher risk of cardiovascular events and hospitalizations. Particularly heart failure hospitalizations are more than twice as high in patients who have anemia compared to those who don't. And then kidney events are even higher in some studies as well. Progression to end-stage kidney disease is higher among patients with CKD, who have anemia than among those who don't. And similarly, endpoints along the way, such as 40% decline in EGFR, or progression across stages of CKD. All of those outcomes are more common or more likely to occur in patients who have anemia than in those who don't.

So now let's look at some new emerging therapies for anemia.

Dr. Singh:
Thanks, Kirsten. And, yes, let's look at some of these new emerging therapies.

In order to think about these therapies, I think it's important to look at the mechanism of action of hypoxia-inducible factor PHIs for the

treatment of anemia in CKD. Again, to summarize, there are two essential components of how these agents work. First, the stabilization of HIF-2 results in the synthesis of erythropoietin by the liver and the kidneys. Data has already demonstrated, even among patients who have failing kidney function and increased kidney fibrosis, endogenous erythropoietin doesn't come from the kidney alone, but comes from the liver as well. And as time goes by, and kidneys basically get completely fibrosed and completely fail to produce erythropoietin, almost all of the erythropoietin production comes from the liver. And this has been shown even among patients who are anephric. This then results in endogenous erythropoietin, which then stimulates the bone marrow to produce red cells.

The other heart of the action of oral HIF is actually occurring in the duodenum. HIF-2 is stabilized by these oral PHIs, and in essence, acts on duodenal cytochrome B or DCYTB to catalyze the conversion of ferric into ferrous, which then acts on divalent metal transporter 1, DMT1, to essentially facilitate the absorption of ferrous through the duodenal channel, ferroportin, into the body.

There are two important players there. One is obviously ceruloplasmin, which is a HIF-regulated copper-carrying ferroxidase that catalyzes the oxidation of ferrous back to ferric, which then is transported around the body by the reticular endothelial system to various storage sites, including the liver, muscle, etcetera.

So, in essence, you have two actions of oral HIF PHI. The first one, I think, has been amply demonstrated in clinical trials, both phase 2 and phase 3, and we'll discuss that in a minute.

The other action, the action on absorption of iron that happens directly, is something that hasn't been quite teased out in clinical trials, but I think, in the next several years will be the subject of quite significant insights.

Let me just now turn to a couple of questions. And I'll pose these questions, and Dr. Johansen, you know, take a take a stab at answering them. I'll join in the discussion. The questions are: what are the potential therapeutic advantages offered by HIF stabilizers? And then second, what is the current status of the various candidates in development?

Dr. Johansen:
Yeah, thank you, Ajay. I think there are two potential therapeutic advantages. The first is oral administration. And that is huge. And I'll talk more about that in a minute. And the second is what you just touched on a little bit is the potential we do I agree, absolutely this needs to be teased out. But the potential that this might improve on our options, and on iron availability as well.

But let's just talk about oral. That sounds like not a big thing, just oral administration, but it really is coming into clinic to get injections bi-weekly, or monthly, is a big burden for my patients. And sometimes it doesn't happen. It's really not uncommon at all that I see patients coming back to clinic who are anemic or below the targets, and who tell me that they couldn't get in to get their injections because their daughter couldn't drive them that day, or they couldn't get time off work. This happens all the time. So having an oral drug that we could give them, that they could take it home, would be just a huge advance.

And the way I know this is, you touched on this earlier, or I touched on this earlier, we both have I think at this point, is that they're not getting these treatments, as I was just saying. Sometimes they're not even being prescribed. In fact, we're doing more transfusion in patients with advanced kidney disease than we are ESA therapy. And so we're just, as a result of these difficulties, we're not getting this therapy to the patient. So having an oral option, I think, is going to be a tremendous advantage.

But I also think that the iron metabolism things that you were just talking about, are fascinating. We all know clinically that our patients don't absorb oral iron very well. I use I.V. iron a lot in my practice for that reason. And because of the GI side effects, but more because it doesn't work. And the possibility that these new - that newer agents, that the HIF PHIs might actually improve on that, is really, really interesting to me. I want to know what your thoughts are?

Dr. Singh:
Yeah, and I think, you know, the, the HIF PHIs, when they began clinical development of the first agent, roxadustat, I think there was an enormous amount of excitement, because of the things you've talked about. The gaps that currently exists with respect to anemia treatment. We have a very large unmet need in patients who are not on dialysis, as you allude to. These patients have to grapple with the bottlenecks that I think we all see as we treat our patients. And that's getting the drug parentally administered in EPO clinics. This seems to have a disproportionate impact on people who are minorities and individuals of a lower socioeconomic class.

Second, the actual use of the drug is difficult because you need a cold chain. In other words, you have to protect the refrigeration of the drug through various stages of manufacturing, transportation, and storage at the site of administration.

And then third is the cost. So you've sort of alluded to that.

The other really big problem is that even among dialysis patients where it's easier to administer the drug, we still don't know what hemoglobin levels to administer to. There's still a debate about whether it's the level of hemoglobin we're correcting to, or the dose of the

drug using high doses of conventional ESAs that's the problem that's generated all these safety concerns. And so we have this excitement about the newer generation of agents that sort of puts all of that to one side and allows our patients to be treated with oral drugs. And with perhaps a new paradigm of how patients are treated, might change things.

Let's now start by taking a deep dive into some of these trials. The first trial I'm going to focus on is OLYMPUS. This is a trial that was looking at the efficacy and safety of roxadustat for the treatment of anemia in patients with CKD not on dialysis. And this was a double-blind phase 3 trial, which randomized non dialysis-dependent CKD patients stage 3 to 5, with a baseline hemoglobin of 10 grams per deciliter to three times a week, roxadustat at a dose of 70 milligrams orally, or placebo. And then they basically titrated doses throughout the study based on the hemoglobin levels.

The primary efficacy endpoint for this trial was mean change from baseline in hemoglobin averaged over weeks 28 to 52, versus placebo, regardless of whether rescue was used.

And shown on this slide in Panel A, you see on the vertical axis, the average LSM for hemoglobin in roxadustat versus placebo, as roxadustat in red, and placebo is in blue. And you can see that in this trial, clearly roxadustat works effectively.

In Panel B again expressed average LSMs for the hemoglobin, on the left hand side and Panel B, you see iron replete patients, and on the right-hand side, you see patients who are not iron replete, and in red is patients on roxa, and blue patients on placebo. And you see that roxa works equally well in patients who were either iron replete, or those who are not iron replete.

When you look at hemoglobin over time, which is shown in Panel C, the vertical axis is the hemoglobin and on the horizontal axis are weeks. And in red, you see the line for roxa, and in blue, the line for placebo. As you would expect in patients treated with a HIF PHI, you get an increase in hemoglobin. And then this happens over the first three months or so, and then the hemoglobin stabilizes.

When these trial results were evaluated by the FDA, one of the concerns the FDA had was this very prompt and steep increase in hemoglobin in the patients randomized to roxa, versus those that were randomized to placebo. And this raised some concerns among our colleagues at the FDA with respect to whether there was a rapid rise in hemoglobin. And they, in fact, presented data at the outcome that related to a higher rate of thrombovenous embolism events and the patient's on roxa. So while you look at this at face value, and say, hey, that's great, we were able to see this quite steep increase in hemoglobin in patients on roxa. In fact, the FDA turned that around and said that that raise concerns about a relationship between rate of rise of hemoglobin and a thrombovenous embolism.

But I think it would be fair to say that this was a protocol to determine rate and rise, right, so if they had slightly different dosing protocol, one wouldn't have seen the rapid rise, and at least hypothetically, one would not have seen the increased rate of thrombovenous embolism.

In the next study that's shown, you can look at ROCKIES, which is the effect of roxadustat for the treatment of anemia in patients with CKD on dialysis here. And this is again, a randomized control trial, approximately 1,051 patients were randomized to a roxadustat, and approximately 1,055 patients were randomized to epoetin alfa. And this is a pooled analysis.

And what you can see is that hemoglobin was very similar between roxadustat and the epoetin alfa. And you didn't see in these dialysis patients that initial, what I think is a dosing protocol-driven rise in hemoglobin that was seen in the previous study, the OLYMPUS trial. And this study was published by Steve Fishbain, and shows for this primary endpoint, again, a hemoglobin endpoint, that drug clearly works.

Now when you look at, in this same trial, safety, you can see two panels on your slide. One is in dialysis-dependent CKD patients and then on the right in non dialysis CKD patients. And we're looking at adverse event summaries in roxadustat versus epoetin alfa. And as you go down this table, you see the results of any AEs, AEs leading to discontinuation of drug, interruption of drug etcetera, etcetera, shown on the left, and any AEs, serious AEs, or any serious AEs with outcomes of death, shown on the right-hand side. And while you do see numerical differences, generally speaking, AEs are not evaluated statistically, these results show that the drug seems to be well tolerated both in patients on roxadustat and epoetin alfa. That's an important observation.

We now move to the next program, which is PROTECT and INNOVATE. These are, as you recall, two studies published in *The New England Journal of Medicine*. What you see in PROTECT are hemoglobin results, but let me just back up by giving you a little bit of an introduction to these studies.

In the PROTECT study, which as I said, was the non-dialysis CKD patients, the goal was to treat patients to a hemoglobin of 10 to 12 grams per deciliter. The patients were enrolled in the United States, where the, you know, enrollment criteria or eligibility criteria was hemoglobin concentration of 8 to 11, and 9 to 12 in other countries. The primary safety endpoints were assessed as time-to-event analyses, and was the first major adverse cardiovascular event or MACE. This was a composite event and it was pooled in these two trials in the U.S. population and in the X-U.S. population have presented as the as the PROTECT-2 program but the other primary

endpoint was change in hemoglobin.

And what you see in this panel on the left-hand side is hemoglobin concentration in the United States, and in X-U.S. shown is untreated patients in Panel A, and untreated patients in Panel B. And clearly, in this study of approximately 3,500 patients, the drug does correct the hemoglobin and you do achieve stability in the hemoglobin.

When you look at the MACE results, which I described as major adverse cardiovascular events, you see four panels on your screen. MACE are the composite in Panel A, and expanded MACE, which adds in other cardiovascular events in Panel B, and death from cardiovascular causes in Panel C, and death from any causes in Panel D. They were looking for whether treatment with vadadustat met the criteria for non-inferiority. And unfortunately, in this trial, it did not. It failed to meet the criteria for non-inferiority. And you can see that there were 382 MACE events for vada, and they were 344 MACE events for darbepoetin. And when you look at, at least what appeared to be the main drivers of this, clearly, there were more individual components of MACE in the patients on vada than those on darbepoetin.

When you look at expanded MACE again, you see that there was an excess numerically of expanded MACE events in patients randomized to vada, versus darbepoetin. But when you look at deaths from cardiovascular causes, there was no difference between the two arms. But when you look at deaths from any causes, there was an excess number of deaths from any cause, obviously this included infection and a variety of other causes of death, there was a numerically higher rate in vada, versus darbepoetin. And you see the hazard ratio there of 1.09 with 95% confidence intervals of 0.93 and 1.27.

So I think the results of this study is probably what explains, in large part, why the FDA issued the complete response letter to Akebia, because they were not convinced as yet. And I'm sure Akebia will have a response to this and so on. But the FDA was not convinced that in non-dialysis patients, that the drug did not have concerns with respect to safety because it didn't meet the criteria for non-inferiority.

When we turn to CKD on dialysis, again, there were two randomized non-inferiority phase 3 trials. These were open label. And the primary safety endpoint was assessed as the time-to-event analysis for the first occurrence of major adverse cardiovascular event, or MACE, composite, as you know, of death from any cause non-fatal MI or non-fatal stroke. And they tested for non-inferiority. The non-inferiority margin in both was 1.25. And in this trial, which had 3,923 patients, they were able to demonstrate a non-inferiority. And what you see here are in Panel A, incidence with respect to hemoglobin, and Panel B is prevalence with respect to hemoglobin. They were able to demonstrate a non-inferiority, have met the criteria for non-inferiority.

The next slide shows the MACE results. Panel A is MACE, Panel B is expanded MACE, Panel C is death from cardiovascular causes, and Panel D is death from any cause. And what you see is essentially the two curves overlap each other completely. This trial demonstrated that vadadustat as compared to darbepoetin did meet the criteria for non-inferiority, i.e. it’s as good as darbepoetin alfa. And so this trial met what were the initial goals that Akebia set with respect to their trials objectives.

We now move to the next trial program, daprodustat. This trial program, I was the first author, Dr. Johansen was also a member of the steering committee. I'm going to now present you data from this trial. The first trial I want you to consider is the ASCEND-ND trial. This is the efficacy of the daprodustat for treatment of anemia patients with CKD who were not analysis. And the data for ND and D and so on, were individual trials, they weren't full trials, as I've shared with respect to either roxadustat or vadadustat. These were individual trials that were conducted worldwide. The hemoglobin target was 10 to 11 grams per deciliter. And this was evaluated between week 28 and week 52. That's the evaluation period.

So seen on this slide, you see the hemoglobin results, and you see the two curves essentially overlap each other. And this was in 3,872 patients that were evaluated. So in this population, in the ND population, when you evaluate the results as shown, and this was an intention-to-treat a population, daprodustat met the criteria for non-inferiority as compared to darbepoetin, and you see the results there.

When you look at the components of MACE in the ND trial, as well as looking at a prespecified secondary principal endpoint of CKD progression, shown here are MACE in Panel A, MACE or thromboembolic events in Panel B, MACE or hospitalization for heart failure in Panel C, death from any cause in Panel D, and the results for CKD progression in the bottom right panel, you see that the MACE results curves are completely indistinguishable. There is no statistically significant difference between the two curves, although numerically slightly higher rates for daprodustat versus darbepoetin, but as I said, not statistically significant. And likewise, the results of death from any cause.

So really met the criteria for non-inferiority for the co-primary endpoint of MACE. But also very similar results with no safety signal when you added in MACE thromboembolic events or MACE with heart failure or death from any cause.

The other thing, and I think this puts to rest this issue, there was no impact of treatment with the investigational agent, daprodustat, as

compared to conventional ESA with respect to CKD progression. And you see the cumulative incident curve, bottom right hand corner, essentially overlapping each other. So the conclusion from this was that daprodustat met the non-inferiority criteria as compared to conventional ESA.

Let's now look at the results of the ASCEND-D trial. This is the efficacy of daprodustat for treatment of anemia in patients with CKD on dialysis. This trial was also a randomized open-label phase 3 trial. And here, entry criteria were hemoglobin patients are between 8 to 11.5 grams per deciliter were randomized to either HIF PHI or epoetin alfa if they were on dialysis, or darbepoetin alfa if these dialysis patients were receiving peritoneal dialysis. Like with the previous trial, we were testing for non-inferiority. The non-inferiority margin was 1.25.

And shown on this slide is the data for 2,964 patients who underwent randomization. And you can see that during the evaluation period, while the hemoglobin curve was slightly higher for patients randomized to daprodustat versus ESA, there was similar hemoglobin control between the two. And the slight difference is, as we discussed with the roxadustat trial earlier, a reflection of the dosing algorithm, but really did meet the criteria for non-inferiority.

When we now turn to MACE, you see the MACE results in Panel A. In Panel B, you see MACE or thromboembolic events, in Panel C, MACE or hospitalization for heart failure, and Panel D, bottom right, you see death from any cause. And in essence, the result is that the cumulative incident curves show that we met the criteria for non-inferiority. Very similar rates for all of the four endpoints that are shown on this slide. So in essence, in non-dialysis patients, daprodustat was as good as conventional ESA.

The first two agents roxadustat and vadadustat, unfortunately, did not pass muster with the FDA, although with roxadustat, it's approved in many different countries around the world. And vadadustat is pending review in the in the European Union. Both agents are approved in Japan. Daprodustat is approved in Japan, and we don't have the results from the FDA review or from the European Medicines Agency Review.

But let me then pose a couple of questions to my colleague, Dr. Johansen. First is, what do we think are the possible explanations for the disparate safety results observed across the three HIF stabilizers that I've discussed? And then what are some of the key unanswered questions that still remain?

Dr. Johansen:
I think there are a number of possible explanations for these differences. And particularly, I imagine you mean the differences in the non-dialysis dependent population safety results? I think one possibility is simply the dosing algorithms. As you pointed out, in the roxadustat trials, they had a fairly rapid rise in hemoglobin, and they were above the patients treated with placebo, certainly. And even in the trial that had an active comparator, they were above. So the dosing algorithm may have been an issue. And I imagine they may think about testing lower doses of the medication.

But in addition, I think we just need to really understand that these are different compounds. They have different molecular structures, they have different half-lives. And they have different - as a result of their different structures, they interact a little differently with the HIF PHIs, and they have different degrees of suppression of different enzymes, inhibition of different enzymes. So it's hard to say, but it may just be related to the differences in these drugs themselves.

Dr. Singh:
What do you think of some of the key unanswered questions that remain, Dr. Johansen?

Dr. Johansen:
Well, as I mentioned earlier, I'm really interested in knowing more about what happens with iron metabolism with these agents. There hasn't been a lot of data. You showed that roxadustat worked equally well among patients who were iron replete, than patients who weren't, which is an exciting and kind of tantalizing finding. But when some of the larger trials have looked at iron utilization, they haven't seen big differences. And I think that's because the studies weren't designed to do that. The studies were designed to evaluate what happened with hemoglobin, and some studies had iron protocols and other studies had less of iron protocols. But in general, iron was managed as we manage iron with ESAs, and that may not be how we want to - how we best manage iron with these new agents. So

I think that's what we need to start to, you know, assuming that they come into use in the clinical environment, I would really like to see us look at whether or not they can reduce the need for iron, or potentially improve the oral availability and then the effectiveness of oral iron and eliminate some of the need or reduce the need for I.V. iron, which, although effective, is just quite difficult to do.

Dr. Singh:
So, let’s look at case one, let me just quickly summarize this as a 68-year-old African American woman with stage 4 CKD, with hypertension and being overweight as a key comorbidities, and she's symptomatic with fatigue and shortness of breath. And I think the

key lab findings is the hemoglobin of 9.5. And of course, the fact that the patient's TSAT is normal at 24% or within the guideline-directed range, and serum ferritin is 120 nanograms per mil. So Dr. Johansen, how would you characterize this patient's level of risk for adverse outcomes?

Dr. Johansen:
I would characterize this patient's risk as high. I'd be very concerned based on the case report that - about her anemia and about her symptoms that could be related to her anemia or could be related to volume overload, even though she didn't have anemia - didn't have edema. So I would characterize her at high risk for hospitalization and for progression of kidney disease on the basis of those things.

Dr. Singh:
Right. And I think, as we haven't discussed this in great detail, but we know from prior observational studies, that anemia is a risk multiplier, if you will, for poor cardiovascular outcomes, poor quality of life, increased hospitalization, increased risk of blood transfusions, and so on. So do you agree that this patient has risks associated with adverse outcomes just by virtue of being anemic?

Dr. Johansen:
Yes, absolutely. That's what I meant. I see it as a flag. A flag that her kidney diseases is advanced enough to be causing that and then that she is at risk of those things. Absolutely.

Dr. Singh:
I'll take the next question, I guess. What are the most pressing concerns with regards to CKD management? I think all of us would agree that this patient has a number of issues going on. One, obviously at the broader level, this patient's got stage 4 kidney disease, we can't lose sight of the fact that we can still modify that rate of progression to try and prevent her from developing end-stage renal disease requiring either dialysis or transplantation. And that means trying to control her blood pressure better, make sure that she's on the right medications to slow progression. We know, of course, that she's on an ACE inhibitor, which is great, which will slow progression but better control of blood pressure, blood pressure 140/70 isn't bad, but could be better. And, you know, the nowadays non-dialysis CKD patients who are not diabetic, the use of an SGLT-2 inhibitor might be something we might consider to try and further slow her rate of progression. In addition, we could control her blood pressure.

But I think the real topic germane to this presentation is the fact that she's anemic. And anemia needs to be addressed. We know that she has iron stores that seem to be reasonably adequate, at least at face value. It is important to know that anemia in this population could be multifactorial. So not only erythropoietin deficiency, but a relative deficiency that might be being impacted by inflammation. So you look very hard for reasons why this patient may be inflamed and not mounting a good erythropoietic response. You'd want to make sure she's not losing blood. And so you'd want to screen out for with fecal occult blood measurements. You do a B12 and folate.

I tend to also try to think about what the patient's diet is. Is she eating healthy foods? Because although her iron stores look adequate, we know from studies that have been done that even those patients with a TSAT in the 20% range with a good ferritin can be iron deficient when you actually look at absolute iron content in the bone marrow when you actually look at it using Prussian blue staining. So while these parameters of iron metabolism show that things are fine, it could be that she's iron deficient and that would also be because she's not taking in enough iron through a diet. So you want to look at that.

But at face value, what I see the primary reason for why she might be anemic is that she has erythropoietin deficiency and you want to correct that. So that's really what I think are the main concerns here.

Dr. Johansen, what do you think are the goals of treatment here? And what type of treatment would you recommend? And what type of target would you, for the hemoglobin particularly would you employ in order to guide management?

Dr. Johansen:
Well you talked a lot about the important goals, the important long-term goals of slowing the progression of her kidney disease by adequately controlling her blood pressure. And I completely agree with that.

But my short-term goals for a patient like this would be to improve how she's feeling, and to keep her out of the hospital. So I would want to be making absolutely sure that she's not volume overloaded by a good physical examination, and then treating with an SGLT-2 inhibitor or other diuretic to try to address any sign of volume overload.

But then, in terms of the anemia that we've been discussing today, I agree with you. I think, I agree with you, for the most part. I tend to be fairly aggressive with iron. And to me those iron studies are borderline, not maybe frankly iron deficient, but borderline. And so given that she has symptoms consistent with anemia, and our hemoglobin is below target, I would start this patient on an ESA. But I would concurrently start iron, certainly to prevent frank iron deficiency. So I would start with oral iron.

But I would even begin a discussion with this patient about the possibility that oral iron might not be enough to keep her from becoming

iron deficient once she receives an ESA and starts making red blood cells. So I usually begin the conversation in a patient like this who I think is in a borderline range, about the possibility that going forward, they're going to need I.V. iron.

In terms of targets, I usually try to keep my patients above 10, if possible. So from a numbers point of view, 10, 10 to 11 is my target range in the clinic. But again, patients are not numbers, and this patient has symptoms. So my most important target for her is symptomatic improvement, more able to carry out her activities without this shortness of breath.

Dr. Singh:
Here we turn to case two now. And let me just quickly summarize case two. This is a 61-year-old Latino man who's on hemodialysis with comorbidities that include hypertension, hyperlipidemia, and type 2 diabetes. The patient is being treated on an ACE inhibitor, statin, DPP4i, erythropoietin iron replacement. Obviously, the use of ACE inhibitors is not here for kidney progression maybe because the patient has some residual renal function and/or for hypertension. And the patient's presenting with fatigue weakness and some shortness of breath. Patient's a little bit hypertensive with a pre-dialysis blood pressure 145/90 has borderline obesity with a BMI of 29 kilogram per meter squared and is a little volume overloaded with 1+ lower extremity edema. He's anemic with a hemoglobin of 9.2, borderline potassium, his phosphorus is reasonably well controlled. He has iron stores that show a TSAT of 25% and a serum ferritin of 840 nanograms per mil. Let me pose the following question to Dr. Johansen, a contrast concerns that you had this patient with those about the first patient?

Dr. Johansen:
Well contrast or maybe compare because I have similar concerns for this patient as I did for the other, that the patient has incompletely treated anemia with symptoms that could be attributable to that, but also appears to have volume overload and hypertension that may not be fully controlled. So in that way, I think those these two patients are quite similar.

Another way in which I think they're a bit similar is that that their iron situation is borderline. And we know that this patient is being treated with iron, although I'm not sure that we know the dose exactly. And so this patient again is not frankly iron deficient, but we know from other studies that iron repletion, even with a ferritin in this range, sometimes improved responsiveness to ESAs. So that's the difference here. This patient is already being treated with an ESA and is not responding or is not adequately treated. So the first consideration is whether or not more iron might help.

What do you think the options are that are available to address the lack of ESA response? And what are the pros and cons of the different strategies you might employ?

Dr. Singh:
Yeah, so I think you're absolutely right. I mean, I think the concerns in this patient, I think, are, is this patient on enough erythropoietin? And generally speaking, that's not something we often question because a lot of patients on dialysis, virtually everyone, is usually part of some sort of protocol in their dialysis center so their hemoglobin is being controlled between 10 to 11 grams per deciliter with an algorithm that calibrates the dosing of erythropoietin. Usually the challenges, as you alluded to is that whether the patients are have sufficient iron on board, because the ferritin, which is quite high in this patient could be an acute phase reactant. And this patient may have ESA hypo-responsiveness. About 8 to 12% of hemodialysis patients are ESA hypo-responsive, depending on how you define ESA hypo-responsiveness. And these patients tend to tend to be so hypo-responsiveness for potentially a variety of reasons; chief of which is that they may not have enough iron on board. And other reasons, of course, you want to exclude are an inflammatory focus. For example, if they have a failed allograft that is a source of inflammation. We don't know what access this patient has. Sometimes, you know, patients who a tunneled dialysis catheter that can be a source of inflammation. You want to look very carefully to see if the patient may have some sort of bedsore or may have some sort of – also if this diabetic patient, maybe an ulcer might be a source of inflammation, so you look for those things. Sometimes patients are not getting enough dialysis, and that can result in erythropoietin – in hypo-responsiveness, or that they may, in fact, have a substantial or severe hypoparathyroidism, which also makes the action of erythropoietin on the bone marrow not so good.

But let's turn our attention to iron issues. There was a trial that I was involved in publishing, called the DRIVE trial. The DRIVE trial stands for dialysis patients response to intravenous iron with elevated ferritin. This was the first author of the study, or the small trial was Dan Coyne. And this was published in JASON, the Journal of American Society of Nephrology in March of 2007. And in this patient, it looked at exactly this type of population, right, patients who had a relatively high ferritin at baseline 500 to 1,200 nanograms per mil, TSAT of less than 25% hemoglobin in less than 11, who are on fairly high doses of erythropoietin. We don't know what the erythropoietin dose was here. But as I said, I'm assuming that it was adequate, if not on the high end.

That trial enrolled 134 patients and randomize these patients to either no iron, the control arm or to ferric gluconate 125 milligrams intravenously, dosed for eight consecutive doses. And what we just discovered, and what we reported in that trial was that iron actually did work when you - in the iron arm, there was a statistically significant hemoglobin response. And that P value was significant,

regardless of what the ferritin was, whether it was less than 800 or greater than 800 nanograms per mil, that the intravenous iron resulted in a greater increase in TSAT in the control patients. And so iron does work in this population.

Now, I am very cautious, even though I was on the paper and part of the executive committee, to overinterpret the results of the DRIVE trial, because it was only in 130 or so patients. But it does suggest or raise the question that maybe this patient is iron deficient and might benefit from empiric dosing of iron.

So what is the treatment I would recommend? I think, obviously, I'd screen for the things that might be causing erythropoietin hyporesponsiveness in this patient. And then if all that came out negative, I would consider an empiric dose of iron in this patient to see if that might improve the hemoglobin in this patient.

Now let's look at some key points of the understanding and treatment of CKD-related anemia. So the key points are, one, anemia is a common complication CKD that exerts a significant negative impact on patient wellbeing, work productivity, and health-related quality of life. Two, patients with CKD-related anemia are at greater risk for poor health outcomes such as volume overload and increased hospitalization and mortality. Three, CKD-related risk is increased among black, Hispanic, and American Indians, and black patients are more likely to have CKD-related anemia. Four, there's a better understanding of the pathophysiology of CKD-related anemia has led to the development of HIF PHIs, which exert their therapeutic effects via stimulation of endogenous EPO production. Five, that in clinical trials HIF PHIs have consistently been shown to be non-inferior to conventional ESAs for hemoglobin efficacy in both dialysis dependent-CKD and non-dialysis-dependent CKD. And then last but not least, six, in terms of safety disparate outcomes, including the risk of MACE, have been reported for roxadustat, vadadustat, and daprodustat. Studies to better characterize the safety of each are currently ongoing.

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