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Evaluating a HIF-PHI for Anemia in In-Center Hemodialysis

Announcer:

You're listening to ReachMD. This program, titled "Evaluating a HIF-PHI for Anemia in In-Center Hemodialysis," is sponsored by Akebia Therapeutics. Here's your host, Dr. Matt Birnholz.

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This presentation reviews the results of studies evaluating a dosing regimen not approved by the U.S. Food and Drug Administration. The information is shared for educational and informational purposes only and is not intended to be professional medical advice.

Dr. Birnholz:

This is ReachMD, and I'm Dr. Matt Birnholz. Today, we're diving into an important topic for nephrologists and dialysis care teams: oral anemia management for patients with chronic kidney disease, or CKD for short, on in-center hemodialysis. And I'm very pleased to be joined by two experts in the field Drs. Gates Colbert and Varshi Broumand.

Dr. Colbert is a nephrologist with the Kidney and Hypertension Associates of Dallas, and he also serves as the President of the Dallas County Medical Society.

Dr. Colbert, thanks for being here today.

Dr. Colbert:

Thank you, it's great to be here.

Dr. Birnholz:

Also with us is Dr. Varshi Broumand, who's a nephrologist at the South Texas Renal Care Group in San Antonio. Dr. Broumand, it's great to have you with us as well.

Dr. Broumand:

Thanks for having us.

Dr. Birnholz:

So, Dr. Colbert, let's begin by setting the stage. How is anemia managed in patients with CKD who are receiving in-center hemodialysis?

Dr. Colbert:

Well first, it's important to note that anemia is a common complication in patients with CKD, particularly those on dialysis.¹ It results from decreased erythropoietin production by the failing kidneys, along with other factors like chronic inflammation and iron deficiency.^{2,3} For more than three decades, the standard of care has been injectable erythropoiesis-stimulating agents, or ESAs, along with intravenous iron supplementation, which are typically administered in the dialysis setting.^{1,4,5} Red blood cell transfusions may also be used in certain clinical situations.^{1,5}

Even more recently, hypoxia-inducible factor prolyl hydroxylase inhibitors, or HIF-PHIs, have emerged as an oral treatment option for anemia associated with CKD. These agents stabilize HIF, supporting endogenous erythropoietin production and erythropoiesis.⁶ And because patients with end-stage kidney disease typically receive in-center hemodialysis three times a week, clinicians often consider how anemia management fits within that established dialysis schedule.^{1,5}

Dr. Birnholz:

Alright, thank you, Dr. Colbert—that's helpful context to know. And now, Dr. Broumand, let's turn to you. When you think about introducing an oral therapy for anemia into dialysis clinics, what workflow or operational considerations come to mind?

Dr. Broumand:

I'm so glad you asked, because that's a really important question. When facilities think about incorporating any oral therapy into the dialysis setting, there are several operational areas that they may need to evaluate.

In my experience, documentation is a key starting point, with clear tracking of administration, hemoglobin trends, iron indices, and dose adjustments. Nursing workflows may also shift with oral therapies, especially if staff are involved in medication handling or observed administration during dialysis. From a practical standpoint, adherence to oral anemia therapies outside the clinic can be variable for my patients, so in-center use may offer more consistent monitoring and follow-up.⁷ Ultimately, implementation will depend on each facility's patient population, staffing, and existing workflow.

Dr. Birnholz:

Excellent, thank you Dr. Broumand, Well, with those insights in mind, I want to shift our focus to the underlying biology. So, Dr. Colbert, can you just help us understand how the HIF pathway is involved in anemia of CKD?

Dr. Colbert:

Of course. The hypoxia-inducible factor, or HIF pathway, is part of the body's innate adaptive response to low cellular oxygenation. And so hypoxia-inducible factors are transcription factors that help regulate this response.^{8,9} Under normal oxygen levels—what we call normoxia—prolyl hydroxylase domain enzymes, or PHD enzymes, add hydroxyl groups to HIF-alpha. This hydroxylation marks HIF-alpha for degradation.¹⁰ But when oxygen levels drop—during hypoxia—these PHD enzymes become inactive because they require oxygen to function. Without active PHD enzymes, HIF-alpha isn't degraded. Instead, it accumulates, moves to the cell nucleus, and activates transcription of genes involved in the adaptive response to hypoxia. In the kidney, that includes increased endogenous erythropoietin production, which stimulates red blood cell production.^{10,11}

And so in patients with CKD, this oxygen-sensing system becomes dysregulated. Structural and functional changes in the kidney alter local oxygen delivery and cellular sensing. Renal cells may adopt what's been described as a “pseudo-normoxic” state, meaning PHD enzymes can remain active even when tissue oxygen levels are low. And that continued HIF degradation limits appropriate erythropoietin production and contributes to anemia.^{3,12}

Dr. Birnholz:

Thank you, Dr. Colbert, that was excellent. So, Dr. Broumand, given what Dr. Colbert just outlined, how do HIF-PHIs work within this pathway?

Dr. Broumand:

Building on what Dr. Colbert described, HIF-PHIs inhibit the PHD enzymes that normally mark HIF-alpha for degradation under normoxic conditions, allowing HIF-alpha to stabilize and accumulate. This pharmacologic ‘hypoxia mimetic’ effect activates HIF-dependent gene transcription, increasing endogenous erythropoietin production and coordinating iron handling in ways that support erythropoiesis in patients with CKD-related anemia.^{6,13}

One example of a HIF-PHI is Vafseo®, the brand name for vadadustat. It's an oral agent that inhibits PHD enzymes from hydroxylating HIF-alpha, leading to increased endogenous erythropoietin production.¹⁴ Vafseo is FDA-approved as a once-daily oral treatment for anemia due to CKD in adults who have been receiving dialysis for at least three months. It's available as 150 and 300-milligram tablets, and the recommended starting dose is 300 milligrams once daily.¹⁴ The dose may be adjusted between 150 and 600 milligrams once daily to maintain hemoglobin levels between 10 and 11 grams per deciliter. That's why hemoglobin should be monitored when initiating or adjusting therapy, and then at least monthly once stable.¹⁴

Dr. Birnholz:

Thank you for that overview, Dr. Broumand. And before we continue our discussion, let's take a moment to review the indications and important safety information for Vafseo.

Announcer:

Vafseo (vadadustat) is an FDA-approved oral HIF-PHI for once daily treatment of anemia due to CKD.

Indication

Treatment of anemia due to chronic kidney disease in adults on dialysis for at least three months.

Limitations of Use

- Not shown to improve quality of life, fatigue, or patient well-being.
- Not indicated as a substitute for red blood cell transfusions for immediate correction of anemia.
- Not indicated in patients with anemia due to chronic kidney disease not on dialysis.

Vafseo (vadadustat) Select Important Safety Information

Boxed Warning

Warning: increased risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access.

Vafseo increases the risk of thrombotic vascular events, including major adverse cardiovascular events (MACE).

Targeting a hemoglobin level greater than 11 g/dL is expected to further increase the risk of death and arterial and venous thrombotic events, as occurs with erythropoietin stimulating agents (ESAs), which also increase erythropoietin levels.

No trial has identified a hemoglobin target level, dose of Vafseo, or dosing strategy that does not increase these risks.

Use the lowest dose of Vafseo sufficient to reduce the need for red blood cell transfusions.

Please stay tuned for more Important Safety Information at the end of this program.

Dr. Birnholz:

Now, we just discussed the FDA-approved once-daily use of vadadustat. And as I understand it, there have been two Phase 3b trials—MO₂DIFY and FO₂CUS—evaluating the efficacy and safety of oral vadadustat three-times-weekly regimens compared to active comparators. Both were open-label, non-inferiority studies in patients with anemia of CKD receiving in-center hemodialysis.^{1,5}

It's important to clarify that Vafseo has not been approved by the FDA for three-times-weekly dosing, and the safety and effectiveness of that regimen have not been established.¹⁴

So, with that in mind, Dr. Colbert, can you tell us more about the MO₂DIFY trial and what it found?

Dr. Colbert:

Absolutely. The MO₂DIFY trial was a 52-week, multicenter study conducted at sites in the US and Europe. It enrolled 319 patients who were on in-center hemodialysis and had been receiving ESAs for anemia management.

Patients were randomized into three groups: vadadustat once daily, vadadustat three-times-weekly, or intravenous darbepoetin alfa. Study treatments were dosed to maintain patients' geographic hemoglobin target: 10 to 11 grams per deciliter in the US and 10 to 12 grams per deciliter in Europe.⁵

Now, if we turn to the findings, mean hemoglobin levels at baseline were generally similar across groups at around 10.2 to 10.3 grams per deciliter. During the primary evaluation period—Weeks 20 through 26—mean hemoglobin levels were approximately 10.2 grams per deciliter in the vadadustat once-daily arm, 10 grams per deciliter in the three-times-weekly arm, and 10.5 grams per deciliter in the darbepoetin alfa arm.⁵

So the mean treatment difference in hemoglobin from baseline at Weeks 20 through 26, compared with darbepoetin alfa, was minus 0.27 grams per deciliter for the vadadustat once-daily arm, with a 95 percent confidence interval of minus 0.55 to 0.01. For the three-times-weekly arm, the difference was minus 0.53 grams per deciliter, with a 95 percent confidence interval of minus 0.8 to minus 0.25. And the pre-specified non-inferiority margin was minus 0.75 grams per deciliter.⁵

Given that, the vadadustat three-times-weekly arm did *not* meet the primary endpoint because the lower bound of the 95 percent confidence interval fell below that non-inferiority margin.⁵

In the published manuscript, the authors noted that patients in the three-times-weekly group received lower mean weekly doses compared with those in the once-daily group, which may have influenced the ability of the three-times-weekly regimen to demonstrate noninferiority relative to darbepoetin alfa.⁵

In terms of safety, the study reported major adverse cardiovascular events along with other side effects. But it's important to note that the trial wasn't designed to determine statistical differences between groups, and the short duration precludes analysis of long-term

effects.⁵

Dr. Birnholz:

Thank you for sharing that data with us, Dr. Colbert. Now, Dr. Broumand, if we take a look at the FO₂CUS trial, how did it build on what was learned from MO₂DIFY?

Dr. Broumand:

So the FO₂CUS trial was also a Phase 3b, open-label, non-inferiority study for 52 weeks, but it was conducted exclusively at US dialysis facilities. It enrolled 456 patients who were on in-center hemodialysis and had been receiving Mircera®.¹ Mircera was selected as the active comparator.¹

Patients were randomized into three groups: vadadustat 600 milligrams three-times-weekly, vadadustat 900 milligrams three-times-weekly, or continued Mircera treatment. These higher starting doses of vadadustat were selected based on the results observed in the three-times-weekly arm of the MO₂DIFY trial.¹

Similar to the MO₂DIFY trial, study treatments were dosed to maintain a target hemoglobin range of 10 to 11 grams per deciliter per study protocol and investigator clinical discretion. Doses in both vadadustat groups could be titrated between 300 and 1,200 milligrams three-times-weekly. There was no protocol-specified maximum dose for the Mircera group.^{1,5}

Dr. Birnholz:

Thank you, Dr. Broumand. And staying with you for just another moment, what did the FO₂CUS trial find in terms of efficacy?

Dr. Broumand:

We saw that mean hemoglobin levels at baseline were generally similar across groups at around 10 to 10.1 grams per deciliter. Patients in the vadadustat three-times-weekly groups experienced an initial decline in hemoglobin through approximately Week 6, which was primarily seen in the 600-milligram group. By around Week 12, hemoglobin levels returned to the target range and then remained relatively stable.

In contrast, patients randomized to the 900-milligram three-times-weekly group generally maintained mean hemoglobin levels above 10 grams per deciliter throughout the study periods.¹ Looking at the primary endpoint, at Weeks 20 through 26, mean hemoglobin levels were approximately 10.1 grams per deciliter in the 600-milligram three-times-weekly group, 10.2 grams per deciliter in the 900-milligram three-times-weekly group, and 10.4 grams per deciliter in the Mircera group.¹

So in terms of efficacy, both three-times-weekly vadadustat dosing regimens met the primary and key secondary noninferiority endpoints compared with Mircera, which was defined as a 95 percent confidence interval lower bound above minus 0.75 grams per deciliter.¹

More specifically, for the primary evaluation period, the treatment difference in mean hemoglobin change from baseline was minus 0.43 grams per deciliter for the 600-milligram three-times-weekly group, with a 95 percent confidence interval of minus 0.67 to minus 0.2. For the 900-milligram three-times-weekly group, the difference was minus 0.23 grams per deciliter, with a 95 percent confidence interval of minus 0.46 to 0.01.¹ And during the secondary evaluation period, which was Weeks 46 through 52, the treatment difference was minus 0.27 grams per deciliter in the 600-milligram group, with a 95 percent confidence interval of minus 0.54 to zero. For the 900-milligram group, the difference was minus 0.38 grams per deciliter, with a 95 percent confidence interval of minus 0.67 and minus 0.1.¹

One additional point worth noting is the dose titration pattern. During the first several weeks, most patients remained on their starting dose. But by Week 8, about 42 percent of patients in the 600-milligram three-times-weekly group were uptitrated to 900 or 1,200 milligrams. That early uptitration paralleled the temporary decline in hemoglobin through Week 6 that I mentioned earlier, with levels returning to target by around Week 12.¹

Lastly, looking at the primary and secondary evaluation periods, roughly half of the patients in the 600-milligram group and about 60 percent of those in the 900-milligram group were receiving 900 or 1,200 milligrams three times a week.¹

Dr. Birnholz:

Thanks for that review, Dr. Broumand. And coming back to you, Dr. Colbert, what did the FO₂CUS trial show in terms of safety?

Dr. Colbert:

Safety was evaluated in all patients who received at least one dose of study drug. Treatment-emergent adverse events occurred in

about 79 percent of patients in the vadadustat three-times-weekly groups and 75 percent of patients in the Mircera group. Serious adverse events occurred in about 44 to 45 percent of patients in all arms.¹

Looking more specifically at cardiovascular events, these occurred in about 11 percent of patients in the vadadustat groups and 13 percent in the Mircera group. However, it's important to mention that cardiovascular events were not adjudicated and were based on the adverse event reporting dataset. The study was not designed to determine statistical differences between treatment groups for safety or cardiovascular outcomes. Formal statistical testing wasn't conducted, and the relatively short duration of the trial and safety follow-up limit interpretation of long-term risk.¹

Dr. Birnholz:

Thanks so much for breaking all of that down for us, Dr. Colbert. Now, we're almost out of time for today, so I'll turn to you, Dr. Broumand, for the final word. What should clinicians take away from these trials in terms of the investigational three-times-weekly dosing research?

Dr. Broumand:

Well, I'd reiterate that vadadustat is approved as a once-daily oral treatment option for anemia in appropriate patients with CKD on dialysis.¹⁴ The three-times-weekly dosing of vadadustat that we discussed today has not been approved by the FDA, and the safety and effectiveness of that regimen have not been established. Ongoing research continues to evaluate its use in patients receiving in-center hemodialysis.^{1,5}

Dr. Birnholz:

Alright, that's a great thought for us to close on.

Before we go, here's some additional important safety information.

Announcer:

CONTRAINDICATIONS

Vafseo is contraindicated in patients with a known hypersensitivity to Vafseo or any of its components, or with uncontrolled hypertension.

WARNINGS & PRECAUTIONS

Increased Risk of Death, Myocardial Infarction, Stroke, Venous Thromboembolism, and Thrombosis of Vascular Access

Patients with cardiovascular or cerebrovascular disease are at increased risk of thrombotic events when taking Vafseo. Avoid use in patients with a history of myocardial infarction, cerebrovascular event, or acute coronary syndrome within the 3 months prior to starting Vafseo.

Hepatotoxicity

Reported in patients taking Vafseo. Measure ALT, AST and bilirubin prior initiation of Vafseo, monthly for the first 6 months, then as clinically indicated. Discontinue Vafseo if ALT or AST is persistently elevated or accompanied by elevated bilirubin.

Hypertension

Worsening hypertension, including hypertensive crisis may occur. Monitor blood pressure. Adjust anti-hypertensive therapy as needed.

Seizures

Seizures have occurred in patients taking Vafseo. Monitor for new-onset seizures, premonitory symptoms, or change in seizure frequency.

Gastrointestinal Erosion

Gastric or esophageal erosions and GI bleeding have been reported. Consider this risk particularly in patients at increased risk for GI erosions.

Malignancy

May have unfavorable effects on cancer growth. Not recommended if active malignancy.

ADVERSE REACTIONS

The most common adverse reactions (occurring in >10% of Vafseo-treated patients) were hypertension and diarrhea.

Please note that this safety information is not comprehensive.

Refer to the [Full Prescribing Information](#), including the BOXED WARNING and Medication Guide, provided during this presentation for complete details.

Dr. Birnholz:

And with those final insights in mind, I'd like to thank my guests, Drs. Colbert and Broumand, for sharing their perspectives on oral anemia management for in-center hemodialysis in CKD.

Dr. Colbert, Dr. Broumand, it was great speaking with you both today.

Dr. Colbert:

Yes, thanks for having me.

Dr. Broumand:

Thank you.

Dr. Birnholz:

For more information on vadadustat and the source publications for the MO₂DIFY and FO₂CUS clinical trials discussed today, please scan the QR codes available in the video version of this program.

Announcer:

This program was sponsored by Akebia Therapeutics. If you missed any part of this discussion, visit [ReachMD.com](#), where you can Be Part of the Knowledge.

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