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Patient-Centered Care for Anemia in CKD: Key Considerations for HIF-PHI Therapy

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is sponsored by Akebia Therapeutics. Here's your host, Dr. Brian McDonough.

Dr. McDonough:
Welcome to *Clinician's Roundtable* on ReachMD. I'm Dr. Brian McDonough, and joining me to discuss how we can select appropriate patients with anemia in chronic kidney disease for hypoxia-inducible factor prolyl hydroxylase inhibitors, also known as HIF-PHIs, are Drs. Jay Wish and Steven Fishbane. Dr. Wish is the Chief Medical Officer for Outpatient Dialysis at Indiana University Hospital and a Professor of Clinical Medicine at Indiana University School of Medicine. Dr. Wish, thanks for being here today.

Dr. Wish:
It's my pleasure.

Dr. McDonough:
Also joining us is Dr. Fishbane, who's the Chief of Nephrology at Northwell Health and a Professor of Medicine at the Zucker School of Medicine at Hofstra University in New York. Dr. Fishbane, it's great to have you with us as well.

Dr. Fishbane:
Thank you. Great to be part of the program.

Dr. McDonough:
So Dr. Wish, let's start off with some background. What does the treatment landscape look like for anemia in chronic kidney disease, or CKD for short?

Dr. Wish:
Well, up until a couple of years ago, the treatment landscape for the treatment of anemia in patients with CKD had been essentially unchanged since 1989 following the FDA approval of the ESAs—erythropoietic-stimulating agents, with erythropoietin being the parent compound. And then we've had a couple of derivatives with longer duration of action since that time. We have iron, which can be available either as an oral administration or an IV administration. And then the treatment of last resort is transfusion.

So these are things that have withstood the test of time pretty well, but there had been an unmet need, especially for patients who had an unsatisfactory response to the ESAs or were inconvenienced by the administration of ESAs, which have to be administered parenterally—either IV or subcutaneously—for an oral alternative. So the HIF-PHIs, which you mentioned in the introduction, do to a certain extent, fill that unmet need. And I think they're an exciting innovation for the treatment of anemia.

Dr. McDonough:
Turning to you now, Dr. Fishbane, are there any patient-specific factors that should inform your approach to managing anemia in CKD?

Dr. Fishbane:
Yeah, thanks for the question. I don't think we do enough of it. I don't think that we consider patient factors and how some patients may be different when it comes to anemia. Part of that is that in dialysis units in particular, a lot of anemia therapy is automated. It's computerized protocols, which are run by nurses. They're very good protocols. They are very helpful. But in some ways, it takes away a little bit of our recognition of certain factors. So, for example, if I have a patient with malignancy, I would probably look at that patient a

little bit differently in terms of doing either ESA or HIF-PHI therapy, probably a little bit more conservatively in terms of hemoglobin targets. Or a patient with a recent stroke, for example, either ESAs or HIF-PHIs—again, I would be treating the patient, but my goals for hemoglobin would be a little bit more conservative. So there are patient-specific factors that could be important.

Dr. McDonough:
And if we look at HIF-PHI therapy specifically, Dr. Wish, what criteria can help us determine whether it's right for a given patient?

Dr. Wish:
I think it's been a one size fits all approach to the treatment of anemia, both for dialysis patients and for non-dialysis patients with CKD. In dialysis setting, it is protocolized. We tend to basically do a cookbook approach, where everybody's treated the same; same hemoglobin targets, same combination of ESAs and IV iron. We tend to push the IV iron very aggressively to try to minimize the ESA dosing because there's cost constraints in terms of the relative cost of these two interventions.

So I think it's important for us to take a step back, look at those patient-specific factors: the responsiveness to the ESA, the requirement for IV iron, the location of the patient, and whether they're a home dialysis patient that may have issues with regarding their access of the parenteral ESAs and the parenteral IV iron compounds. So all these are extremely important considerations in terms of really customizing the therapy.

The HIF-PHIs are a welcome addition to our therapeutic armamentarium because they are orally administered, which makes them much more convenient for the home dialysis patients. And I think it's important to understand that they have additional therapeutic mechanisms of action, just beyond stimulating the production of erythropoietin. They have an important role in terms of iron mobilization. They decrease hepcidin levels, which decreases iron absorption from the GI tract and iron release from storage sites and macrophages in the liver. And as such, they can perhaps overcome functional iron deficiency, which is very common in our CKD patients because of the inflammatory state associated with the CKD.

Dr. McDonough:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Drs. Jay Wish and Steven Fishbane about clinical considerations around selecting patients with anemia associated with chronic kidney disease, or HIF-PHI therapy.

So Dr. Fishbane, let's continue exploring how we can identify patients who may benefit from HIF-PHI therapy. How might this treatment option address unmet needs in ESA hyporesponders?

Dr. Fishbane:
At any given time, if you're taking care of dialysis patients, you'll note that a certain percentage of your patients are hyporesponders. And there's a lot of definitions people have talked about. But generally, if you have somebody whose hemoglobin is not getting to target—or is below 10 despite having to use higher doses of ESAs—that's a hyporesponder. And those patients are important because their symptoms are not being fully addressed with the lower hemoglobin.

But there's also a very strong association between ESA hyporesponse and mortality risk. And because of that, I really think there should be a greater look at this patient population. It's interesting because traditionally, the two most important causes of ESA hyporesponse are iron deficiency, which perhaps is a little bit less today because we use so much iron, and inflammation, which is very important as well. And for the HIF-PHI class of drugs, they kind of fit exactly those two specific causes particularly well. They seem to improve iron availability. And in patients who have inflammation, there's some data from phase 3 programs that show that there may be a potentially opportunistic effect in terms of patients with inflammation. So the biggest causes of an ESA hyporesponse are the ones that are right in the wheelhouse where HIF-PHIs work best. I think it's a special opportunity. So yeah, patients with the ESA hyporesponse are ones that I would definitely be looking at as candidates for treatment with oral HIF-PHI therapy.

Dr. McDonough:
And Dr. Wish, how can HIF-PHI therapy play a role in treating home dialysis patients?

Dr. Wish:
Well, home dialysis has become an important part of our therapeutic landscape in patients with end-stage kidney disease. There have been a variety of Medicare programs that have tried to encourage the use of home dialysis, which is increasing by about 1 to 2 percent a year as a result. So rather than this being a very small, insignificant portion of the ESRD population, home dialysis—when you combine home hemo and peritoneal dialysis—is approaching the high teens and is expected to exceed 20 percent if this trend continues. So that's 1 in 5 patients that could potentially benefit from an oral treatment for their anemia.

Right now, home dialysis patients have to get ESA shots. They have to get injections, which they may have to come to the dialysis clinic

to get. There may be issues in terms of fear of self-injection, and nobody else in the home that's willing to administer the injection. And they often require IV iron. They don't require as much IV iron as hemodialysis patients if they're on peritoneal dialysis, but they still do require some IV iron, and that usually requires coming in again to the dialysis clinic and getting an infusion that can take a couple hours.

So if we give these patients an oral drug, a HIF-PHI, that substitutes for the ESA and perhaps makes oral iron administration more bioavailable, that may decrease the frequency with which they require the trips to the dialysis clinic to get their IV iron. They don't have to worry about the injections, and this is definitely a much more user-friendly approach to the treatment of their anemia.

Dr. McDonough:
Now, as we approach the end of our program, I'll turn to you, Dr. Fishbane, for one last question. Do you have any final insights you'd like to share?

Dr. Fishbane:
I think it's a really exciting time right now in terms of anemia therapy. As Jay pointed out earlier, since 1989, for 35 years, we really have had one primary path of treatment for patients with anemia with kidney disease. Having the HIF-PHI class of drugs available gives us the opportunity now to have choice, to be able to not just be limited to one specific class of agents, but to be able to address patient-specific factors to a greater extent and identify patients where we can use that choice to be able to find opportunities for treatment.

Dr. McDonough:
Thank you. With those key takeaways in mind, I want to thank my guests, Dr. Jay Wish and Steven Fishbane, for joining me to share their insights on selecting patients with anemia in chronic kidney disease for HIF-PHI therapy. Dr. Wish, Dr. Fishbane, it was great having you both on the program.

Dr. Wish:
Thank you so much for having me.

Dr. Fishbane:
Thank you.

Announcer:
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