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HIF-PHIs for Anemia in CKD: A Novel Treatment Approach

Announcer:
You're listening to *Clinician's Roundtable* on ReachMD, and this episode is brought to you by Akebia Therapeutics. And now, here's your host, Dr. Brian McDonough.

Dr. McDonough:
This is *Clinician's Roundtable* on ReachMD. I'm Dr. Brian McDonough, and today I'm joined by Dr. Jay Wish to discuss the hypoxia-inducible factor prolyl hydroxylase, or HIF-PHI pathway, and its role in the treatment of anemia associated with chronic kidney disease, also known as CKD. 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.

Dr. Wish:
It's a pleasure to be here.

Dr. McDonough:
Let's dive right in, Dr. Wish. Can you tell us about the molecular mechanisms of the HIF-PHI pathway?

Dr. Wish:
I'd be happy to. So the HIF, or hypoxia-inducible factor, pathway, was discovered about 20 years ago. And it basically is the way that tissues and cells in aerobic organisms like us adapt to decrease oxygen availability in the area. So if you have hypoxia—because you have chronic lung disease, or you're up in the mountains, or you have low blood pressure and are therefore delivering less oxygen to the tissues, or for whatever reason, there's less oxygen availability—the cells have to adapt to that to survive. And there's a number of ways that they do that. They shift to anaerobic metabolism. They try to improve the delivery of oxygen by increasing the, shall we say, trucks that carry the oxygen, and that is the red cells. So erythropoiesis is one of the adaptations to hypoxia. And then they also try to increase the roads by which those trucks are carrying the oxygen. And that would be angiogenesis—increased development of small vessels. So this is all the package of the response to hypoxia.

Hypoxia-inducible factor is the transcription factor that tells the DNA to transcribe more of these proteins that allow the cells and tissues to adapt to hypoxia. And this has been basically leveraged to improve the production of red blood cells in patients with chronic kidney disease by the use of drugs that inhibit the degradation of the HIF so that you have ongoing production of red cells, despite the fact that the level of oxygen in the tissues is near normal.

Dr. McDonough:
Now, how does this pathway promote endogenous erythropoietin production and facilitate iron metabolism?

Dr. Wish:
Well, HIF comes in two subunits. There's a HIF alpha subunit, which is continuously degraded by prolyl hydroxylase domain enzymes, or PHD enzymes. So in the presence of oxygen, you don't need the hypoxia-inducible factor, and oxygen activates prolyl hydroxylase so that the HIF alpha subunit is degraded, and you don't have the transcription effect of HIF. In the absence of oxygen, the prolyl hydroxylase enzyme is not active, and the HIF alpha subunit survives to migrate to the nucleus to combine with the HIF beta subunit, and it's this heterodimer with HIF alpha and HIF beta, which becomes the transcription factor. So the transcription targets are the genes which code for erythropoietin, and also a variety of genes that code for proteins that affect iron metabolism, iron absorption in the GI tract, and iron release from stores.

So with the use of these HIF prolyl hydroxylase inhibitor drugs, which simulate a hypoxic environment, you have increased erythropoiesis due to the transcription of the erythropoietin gene and the transcription of genes that relate to iron absorption and release. So you have a dual effect on the bone marrow to stimulate the differentiation of stem cells to red cell precursors and the iron availability to synthesize hemoglobin for red cell production.

Dr. McDonough:
You make technical things very easy to understand. I appreciate that. But I want to ask you, how do these mechanisms impact patients who have anemia associated with CKD?

Dr. Wish:
Well, CKD is a state that is associated with anemia. And the reason for that is that the site of the hypoxia-inducible factor activation in the setting of anemia is located primarily in the kidneys, in the peritubular cells. So you have these cells that are around the tubules of the kidney that continuously monitor the availability of oxygen in the tissues. And if oxygen is less available, then there is the downregulation of the prolyl hydroxylase enzyme, the survival of the HIF alpha, and then, again, the increased transcription of erythropoietin.

Patients with chronic kidney disease, because of their damage to the kidneys, have fewer of these hypoxia-sensing erythropoietin-producing cells to begin with. But the state of chronic kidney disease also seems to blunt the hypoxic response. So even in the presence of severe anemia, these sensors don't get the message. There's fewer sensors. The sensors are not as sensitive to the hypoxia, and therefore, severe anemia can persist. In a person with normal kidneys, that anemia would be sensed by these hypoxia-sensing cells in the kidney, and that would lead to increased erythropoietin production. That just doesn't happen in patients with chronic kidney disease.

So as I said, hypoxia-inducible factor is a transcription factor for erythropoietin. So if our approach here is to try to decrease the need for exogenous erythropoietin and promote the synthesis of endogenous erythropoietin, then our goal is to inhibit prolyl hydroxylase, and that's why this class of drugs is called prolyl hydroxylase inhibitors. So they basically are small molecules that can be administered orally, unlike exogenous erythropoietin and its analogs. And these oral drugs, by inhibiting prolyl hydroxylase, allow the HIF alpha subunit not to be degraded so that it can migrate to the nucleus, form that heterodimer, and promote the transcription of these proteins, such as erythropoietin and the iron mobilization proteins as well.

So it is a double negative, and it can be confusing. What we're doing is inhibiting the inhibitor and thereby promoting the HIF pathway in the setting of the use of these drugs.

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 Dr. Jay Wish about the hypoxia-inducible factor prolyl hydroxylase, or HIF-PHI, pathway in patients with anemia in chronic kidney disease.

How does this approach differ from traditional anemia treatments like erythropoiesis-stimulating agents and IV iron?

Dr. Wish:
So it basically replaces the ESAs because we're now promoting endogenous erythropoietin production through the transcription factor which is HIF, as opposed to administering erythropoietin analogs exogenously. So the traditional treatment of CKD-associated anemia for the last 35 plus years—since 1989 when the first erythropoietin-stimulating agent, or ESA, was approved—was to administer these ESAs on a regular basis to make up for the fact that these diseased kidneys are not making erythropoietin. So what we're doing is tricking the kidney into thinking that there's more hypoxia than there is and thereby stimulating these endogenous genes to synthesize erythropoietin and the iron mobilization proteins.

So this can have a dual effect. Number one, you substitute endogenous erythropoietin production for exogenous erythropoietin. But the other beneficial effect of these agents is that by stimulating the transcription of these iron-related proteins, you can have improved iron release from stores, so you can overcome some of that functional iron deficiency that often occurs in patients with chronic kidney disease because of the inflammatory state of the CKD itself. And you can also promote the absorption of more oral iron. So for patients who, for instance, are on home dialysis, giving these HIF-PHIs as opposed to exogenous ESAs may improve oral iron absorption and decrease the need for IV iron administration, which in-home dialysis patients can be inconvenient.

Dr. McDonough:
As we approach the end of our program, Dr. Wish, do you have any final takeaways you'd like to share?

Dr. Wish:
So the current treatment for anemia in patients with chronic kidney disease has served us reasonably well over the last 36 years. We had the ESAs. We know how to use them pretty well. Not everybody responds as much to the ESAs as other patients, so there is still a

certain amount of frustration in the patients who have what we call ESA hypo-responsiveness, who either require high doses of ESAs or do not achieve target hemoglobin levels. And there's also the issue in terms of all the IV iron that we often have to give our dialysis patients to overcome this functional iron deficiency due to the inflammatory state.

So this new class of drugs, this HIF-PHI class, is extremely promising in filling the unmet need for the home dialysis patients who have the inconvenience of injections of ESAs and IV iron, as well as in-center dialysis patients who may not respond as much as we would like to the traditional therapies.

And just to take an example of why traditional therapies don't work as well as we like is the fact that almost 25 percent of dialysis patients receive a blood transfusion. And blood transfusions are the treatment of anemia that are last resort and are really to be avoided because they sensitize the patients to human antigens and limit the pool of potential donors for kidney transplantation. So since kidney transplant is ultimately the goal in many, if not most, of our dialysis patients, decreasing the number of potential donors is obviously a downside that we would like to avoid. And if we get better, more effective, and more convenient treatment of their anemia, decreasing the need for blood transfusions, then perhaps we can get more of our patients transplanted and get them to a quality of life that clearly would be superior to chronic dialysis.

Dr. McDonough:
With those key insights in mind, I want to thank my guest, Dr. Jay Wish, for joining me to discuss how the HIF-PHI pathway can help us manage anemia associated with chronic kidney disease. Dr. Wish, it was great having you on the program.

Dr. Wish:
My pleasure. Thanks for inviting me.

Announcer:
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