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Decoding the HIF Pathway: Implications for Anemia in CKD

Announcer:

You're listening to *Clinician's Roundtable* on ReachMD, and this episode is sponsored by Akebia Therapeutics Medical Affairs. Here's your host, Dr. Charles Turck.

Dr. Turck:

This is *Clinician's Roundtable* on ReachMD, and I'm Dr. Charles Turck. Joining me to discuss the role of the hypoxia-inducible factor, or HIF, pathway in the pathogenesis of anemia due to chronic kidney disease is Dr. Jay Wish. Not only is Dr. Wish a Professor of Clinical Medicine at Indiana University, but he is also the Chief Medical Officer for outpatient dialysis at Indiana University Health. Dr. Wish, welcome to program.

Dr. Wish:

Thank you very much. It's a pleasure to be here.

Dr. Turck:

So, Dr. Wish, would you give our audience an overview of how chronic kidney disease, or CKD, can cause anemia?

Dr. Wish:

I'd be happy to. Our views of the mechanism of anemia development in patients with chronic kidney disease has evolved with the science over the last 40 or so years. We used to think naively that because the kidneys are the source of erythropoietin, the hormone that stimulates the bone marrow to produce red blood cells, that kidney disease by decreasing erythropoietin production was responsible for anemia purely due to erythropoietin deficiency. In 1989, the use of a biologic form of erythropoietin was approved by the FDA, and we found in the last 30-plus years that this has not been the panacea that we expected for the treatment of anemia. There still remain many patients who receive erythropoietin who do not achieve target hemoglobin levels, and there's a significant fraction of patients who have CKD-associated anemia that are unresponsive or hyporesponsive to erythropoietin.

So this has led to increased understanding that anemia in patients with chronic kidney disease is multifactorial and one of the major villains in this process is actually inflammation. Inflammation increases hepcidin production by the liver, which decreases the availability of iron to act as a substrate for the synthesis of hemoglobin in the bone marrow. In addition, over the last 20 or so years, we've come to understand the role of the hypoxia-inducible factor, or HIF, pathway in the pathophysiology of red blood cell production. And this understanding has led to the development of new approaches for the treatment of anemia over the last 5 or 6 years.

Dr. Turck:

Now continuing to zero in on the HIF pathway, what is it and what's its connection to anemia and CKD?

Dr. Wish:

Hypoxia-inducible factor is actually a dimer. It is two separate proteins that combine in the nucleus to stimulate the transcription of a variety of genes that are related to red blood cell production. These include not only the erythropoietin gene, but also genes that are required for increased absorption of iron and for the transport of iron from storage sites to the bone marrow. In the presence of hypoxia, a variety of tissues will have to adapt to the hypoxia by a variety of pathways. This includes a shift to more anaerobic forms of metabolism, increase in erythropoiesis to shunt more oxygen to the tissues, as well as an increase in angiogenesis to provide more

roadways, if you will, for those red cells who deliver oxygen to the tissue. So understanding the HIF pathway has allowed us to leverage that very pathway to increase the production of red blood cells through mechanisms other than the synthetic forms of erythropoietin that we've been using over the last 35 or so years.

Dr. Turck:

Well, speaking of that, how does our understanding of this HIF pathway impact the management of CKD-related anemia?

Dr. Wish:

Well, the HIF pathway, as I said, involves not only the production of erythropoietin through the stimulation of the gene that transcribes erythropoietin, but as I said, it increases the mobilization of iron. And since inflammation, as I said before, is a major confounding factor for the anemia in patients with chronic kidney disease, our ability to improve iron mobilization through the stimulation of the HIF pathway allows us to have a more, shall we say, a complete erythropoietic response with the use of drugs that help stimulate the production of HIF.

Now I should point out that HIF, as I said, has two subunits. There's an alpha subunit, which is normally degraded by an enzyme called prolyl hydroxylase, or PH. And this new class of drugs inhibit the degradation of proline hydroxylase. They're called prolyl hydroxylase inhibitors, or PHIs. And in so doing, they allow the HIF alpha subunit to survive where it migrates to the nucleus of the cells. It dimerizes with HIF beta, which is always present, and then this HIF heterodimer increases the transcription of the proteins that I mentioned before. That includes not only the erythropoietin gene, but a variety of iron specific genes. A number of these genes such as transferrin, the transfer receptor, and several proteins that are involved in the iron absorption through the duodenum will work together to deliver more iron to the bone marrow. The problem with ESAs, or erythropoietic stimulating agents, alone is that they do not address the functional iron deficiency that occurs in the setting of inflammation. And the promising thing about this new class of drugs, the HIF prolyl hydroxylase inhibitors, is that by increasing the transcription of these iron-related genes, not only do we get more erythropoietin through its gene transcription, but more iron availability to the bone marrow to allow for the production of red blood cells. The other nice thing is having choices, and as I said over the last 35 years, our choices with regards to anemia management have basically been limited to the ESAs and iron supplements: oral iron supplements and intravenous iron supplements. So having the choice of a new class of agents allows us to be more specific and personalized in terms of the ability to treat the specific issues that cause the anemia in an individual patient.

Dr. Turck:

For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Jay Wish about the hypoxia-inducible factor pathway in chronic kidney disease.

Now, Dr. Wish, there seems to be a range of factors that can influence the activation of HIF, so does that complexity create any unique challenges for you when managing these patients?

Dr. Wish:

Well again, anemia is a spectrum of issues that may contribute to different degrees in different patients. So looking at the dialysis patient population in particular, where anemia is the most prevalent as 90-plus percent of patients who are on dialysis have anemia, every patient is different in terms of their responsiveness to ESAs, in terms of their need for intravenous iron supplementation, et cetera. So we have a subclass of patients within the dialysis population that are termed erythropoiesis-stimulating agents hyporesponsive, or ESA hyporesponsiveness. And this is defined as patients who require large doses of ESAs or who on usual doses of ESAs do not achieve target hemoglobin levels. So there's a resistance to ESAs, and in most of these patients when we do laboratory testing with regards to iron, what we find is that they have very high serum ferritin levels, representing high levels of storage iron, and very low transferrin saturation levels, representing low levels of circulating iron. This disconnect, if you will, has often been called the RE blockade because there is a blockade in the release of iron from storage in the reticuloendothelial system to the transferrin carrier protein, which allows it to be delivered to the bone marrow. The HIF-PHIs seem to a certain extent, at least based on laboratory parameters, decrease this RE blockade primarily through the downregulation of hepcidin. So what we see with most of these HIF-PHIs is a decrease in ferritin levels and an increase or at least a stabilization of transferrin saturation levels because what happens at the same time is that the transferrin saturation is obviously the quotient between the circulating iron and the iron carrier protein. The iron goes up, the transferrin goes up often to a same degree so that the transferrin saturation doesn't really change, but there's still more iron available for delivery to the bone marrow. So it'll often happen in patients with this situation who were given a HIF-PHI is that you have a better response than you would with the ESA alone because of the release of iron from storage sites; again, these are often inflamed patients that have a variety of inflammatory conditions. What we frequently see is dialysis catheters that have their own biofilm. We frequently this in diabetic patients

who have vascular disease and ischemic toes. We frequently see in patients with poor dentition who have periodontal disease, but whenever you see this inflammatory picture of high ferritins and low TSATs, this is potentially a role for HIF-PHIs to decrease the ESA hyporesponsiveness and get a better response in the hemoglobin level towards the target range.

Dr. Turck:

And given the challenges that we've just been discussing, are there any other ways that we can leverage what's known about the HIF pathway to overcome those obstacles and improve patient care?

Dr. Wish:

Well, one of the things that I didn't mention about HIF-PHIs is their oral route of administration. And this is a significant advantage versus the ESAs in many patients because the ESAs require parenteral administration; they have to be injected either intravenously frequently on the dialysis circuit if the patient is on in-center hemodialysis or they're administered subcutaneously in home dialysis patients or in patients with non-dialysis CKD. HIF-PHIs are small molecules, as I said; they can be administered orally. So for instance, in a home dialysis patient who may have to come to the dialysis center every week or two or month, depending upon the ESA prescription to get their ESA injection, the ability to take an oral agent can be a significant advantage, especially if there are logistical barriers to their being able to get to the dialysis center or if they just don't like shots. And there are many patients that don't like injections, they don't like needles.

So the ability to administer a drug that's effective in treating their anemia in a daily or twice weekly or three times weekly oral fashion, depending upon the pharmacokinetics of the drug, is a significant advantage to the patient; again, this is all patient-centered care. What we're trying to achieve here with the treatment of anemia in our patients with chronic kidney disease is number one, addressing what are the barriers to achieving target hemoglobin levels in that particular individual? Is it barriers to the access of the drug? Is it barriers to the patient's tolerance of the drug? Is it barriers in terms of inflammatory blockade of iron absorption or iron mobilization? And then we try to choose a treatment regimen that is not only effective, but is also patient friendly, something the patient has access to and something the patient is willing to take.

Dr. Turck:

Now we're almost out of time for today, Dr. Wish, but before we close, are there any other key takeaways you'd like to share on the biochemistry of CKD-related anemia?

Dr. Wish:

Well, the main thing is again, our increased knowledge in terms of the mechanism of the anemia. Our understanding of anemia has grown tremendously from the 1980s where we thought that it was simply due to erythropoietin deficiency to our now understanding not only the role of inflammation and the role of functional iron deficiency, but also the mechanisms by which we can leverage our own HIF pathway, our own built-in defense against hypoxia tissues to be able to increase the transcription of those very proteins that are important to overcome the very barriers to the production of red blood cells in the setting of chronic kidney disease. This is very exciting science. It's obviously just the very beginning in terms of our understanding and our being able to develop additional drugs that leverage some other pathways in terms of the production of hepcidin or other ways to overcome this inflammatory blockade to red cell production in patients with chronic kidney disease. And I'm looking forward, as are many of my colleagues, to additional discoveries and additional therapeutic agents that leverage those scientific discoveries over the next 5 to 10 years.

Dr. Turck:

Well, given the importance of the HIF pathway, I want to thank my guest, Dr. Jay Wish, for joining me to discuss the critical role it plays in the management of chronic kidney disease. Dr. Wish, it was great having you on the program.

Dr. Wish:

It's been my pleasure. Thanks so much for having me.

Announcer:

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