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Improved Patient Outcomes Needed STAT! for Anemia in Chronic Kidney Disease

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[CHAPTER 1]

Dr. Vega:
Welcome to the "Improved Patient Outcomes Needed Stat! for Anemia in Chronic Kidney Disease" educational series. In the first chapter, we'll walk through the challenges of identifying and treating anemia in a patient with chronic kidney disease, or CKD.

Coming to you from the ReachMD studios in Fort Washington, Pennsylvania, this is CME on ReachMD, and I'm Dr. Charles Vega. Here with me today is Dr. Rajeev Raghavan. Rajeev, it's great to see you.

Dr. Raghavan:
Wonderful, thank you so much for having me, Dr. Vega.

Dr. Vega:
So let's get started. Dr. Raghavan, why is a timely assessment and diagnosis of anemia in CKD so important, and also, why is it so challenging?

Dr. Raghavan:
Yeah, that's a great question. Anemia in chronic kidney disease is one that's – it's a very prevalent condition. Stage 1 chronic kidney disease, which the very earliest stage anemias seem to affect about 8% of patients, and as CKD progresses, as the eGFR [estimated glomerular filtration rate] declines, seemingly more and more patients are affected with anemia in chronic kidney disease, such that by stage 5 chronic kidney disease, over 50%-60% of patients can be affected with anemia. So it becomes, one, very prevalent. Second is associated with increased mortality, which of course is very alarming for all of us, and we want to make sure that we address and treat this in a timely manner.

Number 3 is that the diagnostic challenges include that, like many of our diseases in kidney disease, it does require a laboratory diagnosis, and so there are a certain set of labs, for example, the CBC [complete blood count], looking at the MCV [mean corpuscular volume], which gives that index about the size of your red blood cells; looking at iron panel including the ferritin and iron and TIBC [total iron-binding capacity]; sometimes getting B12 or folic level; and in appropriate patients, a reticulocyte index. And so all these laboratory measurements are also needed to help kind of characterize the anemia and to find out what the best appropriate treatment is for your patient.

Dr. Vega:
Yeah, I find that sometimes we might dismiss mild anemia in folks with CKD because oftentimes they don't just have chronic kidney

disease. They may have heart failure, they have diabetes, hypertension – well, this is anemia of chronic disease; it's probably not that consequential. Their hemoglobin's 9.7, you know, they're not fainting or getting presyncope, and so it must be okay. Well, it's not. Those patients very frequently are having fatigue and exercise intolerance and difficulty concentrating, all of those types of symptoms that we associate with having anemia, and that leads to disability. They're not as efficient in their work lives, they're not as efficient in their home lives, and that's a significant cost to all of us.

And then finally, you mentioned as well – you're absolutely right – that anemia in CKD is associated – independently, in and of itself – with a higher risk of mortality and especially when the hemoglobin drops below 10. That's where you really see a separation versus folks with chronic kidney disease and a normal hemoglobin level.

So there's a lot of reasons to take it seriously, yet it's still underdiagnosed, under recognized, and undertreated. Any other comments on that?

Dr. Raghavan:
No, I think you bring up great points. Those symptoms are really the classic symptoms, and I think one thing that oftentimes we forget to do is to ask the family members. A lot of times, the patients will power through their anemia, and they'll chalk it up to, you know, diabetes or old age or I'm just working long hours. And really, when you get the family involved, they'll say, "You know, he or she is just not quite the same for the last couple months." And if you notice that that happens along the same side as a decline in hemoglobin, then it may further prompt you to treat and take anemia a little bit more seriously.

Dr. Vega:
Yeah, it's great to have reporters in primary care, especially family medicine that might be taking care of the spouse and the adult children of the individual with CKD, so that's a point very well taken. I think it's also important that you're thinking about screening as the – is absolutely right, checking iron levels, reticulocyte count, be considering B12 and folate. Make sure there isn't another cause of anemia for these folks, because there's a certain number of individuals with anemia that also have colorectal cancer, so we want to make sure that there are routine screenings that can promote anemia, just like we would in any, you know, middle-aged or older adult, we're going to want to make sure those are up to date.

And that means, you know, getting them in for a colonoscopy. This is not a time to do a fit test. We really want a gold standard test for colorectal cancer screening. But it is another challenge, especially in somebody who's already suffering fatigue, and having a lot of specialist appointments at this point, you know, to get a colonoscopy is another challenge, and nobody's that excited about going to a colonoscopy, right?

Dr. Raghavan:
Yeah, absolutely.

Now one thing I want to talk about is a little bit about the standard of care, which is really important to mention here, is that a lot of times when you have these patients, they do have a deficiency of iron, and so it's very important to recognize that and to treat iron. And a lot of times, you can treat with oral iron, which, you know, is easily available over the counter. So one 324-mg tablet of, say, iron sulfate taken twice a day does provide enough elemental iron to raise the hemoglobin over a period of a few months. So that's very important. Secondly, we do want to try and avoid red blood cell transfusions. A lot of our patients with CKD, we want to make sure they're good transplant candidates, and exposing them to different other blood products does give them a risk of forming antibodies. We really do want to try and avoid blood transfusions. And then secondly, once we find that the patient is iron replete and their B12 has been corrected and their hemoglobin still remains low, that's where we start to think about other treatments, which include a class of drugs called erythropoiesis-stimulating agents, or ESAs.

Dr. Vega:
So, to me, that's the time we're going to refer over to you and possibly hematology as well, but likely you see so much of it in nephrology. It's something that's in your wheelhouse. Would you want to see a patient sooner than that, or would you like to see a trial with oral iron and getting iron stores up towards normal before getting that referral?

Dr. Raghavan:
Yeah, and that's a great question. I typically like to see patients when they get to stage 3B chronic kidney disease which is, again, when the eGFR is below 45 mL/min. And that's oftentimes when we do find anemia of chronic kidney disease starts to rear its head. So most of the time, I've already established care with the patients and that I recognize anemia and start to treat and do the appropriate testing.

Dr. Vega:
And, yeah, when you were mentioning standard of care, we want to be screening folks with CKD routinely for anemia, so that means starting at the level of CKD 3 they should be getting a CBC at least annually, but as they move into more severe CKD – stage 4, stage 5

– they should be getting at least every 6 months, and this is at least. If they're symptomatic or you're seeing some kind of fluctuation you can't explain, it's a pretty easy test to order a CBC. Once they're on dialysis, they're getting labs all the time, and so really, the minimum standard there would be every 3 months a patient's getting examined for CKD. It's hard in the milieu of different types of conditions we have to take care of in folks with CKD, so it can be a challenge when you're trying to balance, you know, maybe their shoulder pain and their health maintenance along with their hypertension, diabetes, and chronic kidney disease. That's why I really feel like having some kind of prompt or decision aid built into the electronic health record can be a real benefit. When it's done smartly, those reminders can be absolutely a game changer for patients in terms of getting them on the right therapy and then getting them back to, you know, the things they want to do, right?

Dr. Raghavan:
Absolutely.

Dr. Vega:
Okay. Any other challenges that you can think of or take-home points you'd like to make when it comes to the diagnosis and implications of anemia in CKD?

Dr. Raghavan:
No, I think we talked about some really great things here. I think the big takeaway is that anemia is very highly prevalent, associated with high mortality, and can be treated, honestly, can be treated quite easily by providers who are in primary care as well as, of course, by specialists in nephrology, like myself.

Dr. Vega:
In Chapter 2, we're going to be discussing the treatment burden of anemia in CKD both on patients and care partners because, as I mentioned, just having chronic kidney disease along with hypertension and diabetes, it's automatic polypharmacy. And then to be using, particularly, parenteral therapies on top of that, often delivered in a healthcare setting, can be, one, time-consuming and difficult for a lot of patients. So we'll be talking about what's currently available and also be looking forward to some newer agents which might ease that burden back. So please stay tuned and thank you for joining us.

[CHAPTER 2]

Dr. Vega:
Welcome back. In the first chapter, we learned how to identify and treat anemia in CKD. Now we're looking at the treatment burden faced by both patients and their care partners.

Dr. Raghavan, now that we understand how to identify these patients and what to expect from the current standard of care, can you discuss the need for improved management of anemia in CKD?

Dr. Raghavan:
Yeah, absolutely. You know, I'm a nephrologist, Chuck, and I love pathophysiology. I think anyone would say that we're the nerds of internal medicine, so I think before we kind of dive into it, if it's okay with you, I'd like to talk a little bit about the pathophysiology of iron metabolism and what makes this a little bit more complex – not really as simple as just treating anemia. There is – as I like to teach the students and the residents I work with, every electrolyte in the body has a hormone, and for iron, the hormone that controls it is one called hepcidin. And this is one that probably not a lot of people are familiar with, but hepcidin is upregulated in inflammation, which we know many of our patients have a lot of inflammation from their kidney disease, the diabetes, the other comorbid conditions they have.

And hepcidin has a very unique role because it affects the way that iron is utilized and incorporated into blood cells, of which iron is the primary component. And so many of our patients with chronic kidney disease, because of the increased inflammation, they have increased levels of hepcidin, which further impairs their ability to use iron and to make new red blood cells, and so this is what we call a functional impairment of erythropoiesis. In addition, as we talked about earlier, many of our patients may have increased blood loss, whether through increased needle sticks, through gastrointestinal bleeding, and that can lead to absolute loss of iron, and so our patients really are at risk of iron deficiency for these 2 reasons. That's why, as we mentioned in Chapter 1, really checking an iron panel and making sure that they're at the target indices is really first and foremost in treating anemia of chronic kidney disease.

Dr. Vega:
So, Rajeev, should we be checking a hepcidin level as well in these patients? Does – because that's not something I'm doing routinely in my practice. Is that a very specialized lab?

Dr. Raghavan:
You know, Chuck, I don't even know if there's a lab that does that right now. I don't think – I don't think that test is ready for prime time

yet, but certainly, you know, fast-forward several years, we may be there.

Dr. Vega:
And maybe that's a way to identify who's at risk for progressing to anemia in chronic kidney disease. And, gosh, I was thinking, you know, with that chronic inflammation, which every patient has with CKD, it's by definition an inflammatory state, is it worthwhile just to put patients on iron orally prophylactically, even when their iron stores are normal? Is that something you would advise? Because we are seeing, in primary care, a lot of folks who have very mild stages of CKD.

Dr. Raghavan:
Yeah, so, I mean, I think as far astreating iron goes, remember we defined anemia as a hemoglobin less than 13 in men, and 12 in women, and so if you keep that strict definition of anemia, if a patient is at or below those standards, again, oral iron is fairly innocuous and fairly easy to take, and so definitely, I would agree with treating patients who are very close to that threshold. As far as when we think about getting them iron-replete and thinking about once they are iron-replete, whether or not to treat with erythropoiesis-stimulating agents, the guidelines typically suggest that when the hemoglobin is less than 10 and the patient is symptomatic, or definitely if the patient's hemoglobin is less than 9, those are the 2 levels at which we really want to think about adding on top of iron supplementation, adding an erythropoiesis-stimulating agent, or ESA for short.

Dr. Vega:
That's a great point about ESAs, and I completely agree on the iron. But we do know that patients, for a variety of reasons, including it does have side effects – mostly GI side effects, aren't able to tolerate oral iron. And adding an ESA before iron stores are replete is a mistake. And for those patients, there's IV iron therapies, and I think that, especially in primary care because we're not as familiar, we don't have a lot of folks on IV iron, it – we remember that's associated with a history of having some severe reactions, potentially life-threatening, especially for frail and older adults. But the new generation of parenteral iron therapies has a much lower risk of those severe reactions and can actually work very quickly to get iron stores replete so we can start the ESA, and it's actually going to be effective.

But this is really delving into your world, Rajeev, so please go ahead. I'd love to hear your thoughts.

Dr. Raghavan:
No, I think you're absolutely right. There are a lot of patients who, either due to the ease of iron administration parenterally or just the side effect of taking oral iron, which, you know, has a very constipating effect on several individuals, doing IV therapy is certainly an option, and as you mentioned, the newer agents, some of which have much larger amounts of iron – 500 to 750 mg per dose, which is much higher than some of the previous formulations that you were alluding to earlier.

So I think it's very important to keep in mind that there is parenteral iron supplementation which can work for some patients.

Dr. Vega:
At the same time, now we're talking about parenteral iron therapy, parenteral ESA therapy. This is a lot of visits for patients, and many times they are being brought in by the people who are their supporters. Is there any way to alleviate that treatment burden? Because I think it is significant, and a lot of patients will miss appointments. You know, they've been carefully orchestrated, and the team is ready to go. A patient can't make it in because they lost their ride or they're sleeping and they over – you know, they overslept through the appointment. Any recommendations to overcome some of those types of challenges?

Dr. Raghavan:
No, those are a lot of challenges, and especially when we think about ESAs, there's the added burden of many of the ESAs that are – I mean, all the ESAs available right now are – require, you know subcutaneous injection, which can be quite painful for some patients, not just physically but also just the thought of doing injections. And so adding to that and the other insurance hurdles that we're all quite familiar with, it does become very challenging for physicians to manage these patients. And certainly we, you know, really do hope that there's some better options in the future for our patients with anemia in chronic kidney disease who do require treatment with ESAs.

Dr. Vega:
And one challenge for my patients is every injection must be insulin. And so maybe if they're on a GLP-1 agonist and perhaps they're taking insulin as well, and then you add the ESA, you know, they're not sure exactly which one they're taking, and obviously we want to be very clear on dosing and what the role for those individual drugs might be. And so I think that is a challenge, and having, as you said earlier, enlisting those supporters so they understand how important this is, when we're talking about lowering the risk of mortality, when we're talking about improved function, and really helping patients to live their complete lives, yeah, I think it's worth it to consider these next steps when we're talking about higher-dose iron or parenteral iron and thinking about ESAs as well. ESAs definitely reduce the risk of transfusions, which we want to avoid. That's another thing that really, one, exposes some patients to some health risks. There can be

severe reactions – rare, but they do happen. But also, it's just another burden, and when you talk about the sick role – patients feeling more sick – getting regular transfusions is part of that picture as well. ESAs aren't as effective, though, in necessarily improving, say, mortality outcomes or cardiovascular outcomes. That's my understanding.

Is that true, Rajeev?

Dr. Raghavan:
Yeah, that's true. I mean, ESAs do have a risk in the sense that all – several trials, notably in the early 2000s, did look at using ESAs to treat to normal hemoglobin, so hemoglobin of say above 12 or above 13, as we mentioned earlier. All these trials did have a higher incidence of strokes, higher incidences of cardiovascular events, increased mortality, and so the current treatment guidelines really do recommend keeping the hemoglobin between 10 and 11.5 when we're treating patients who have anemia of chronic kidney disease. And the jury is still out whether it's due to the medications themselves or whether it was just due to the increased target of hemoglobin, which now, thankfully, we're really not advising to go above 11.5.

Dr. Vega:
Right. I don't see that changing, even as we potentially move into a new era where we're using different agents in terms of improving that anemia.

So that's a great close, Dr. Raghavan. You know you're the best. I look forward to speaking with you in Chapter 3, where we are going to be discussing these emerging treatment options for patients with anemia in CKD. And thank you to our audience as well. Please stay tuned and we'll see you there.

[CHAPTER 3]

Dr. Vega:
Welcome back. In Chapter 2, we reviewed the drawbacks of current treatments for anemia in CKD. Now in Chapter 3, we're discussing a new treatment and what this may mean for clinical practice and our patients.

This is an exciting topic, so let's dive right in. Hypoxia-induced factor prolyl hydroxylase inhibitors, or HIF-PHIs, represent a new class of pharmacotherapy.

Dr. Raghavan is back. What can you tell us about these agents and their potential impact on patient outcomes?

Dr. Raghavan:
Yeah, thank you, Chuck. This new class of drugs, which you said it perfectly – the HIF-PHIs, they're really exciting for us as nephrologists. When we think of erythropoiesis-stimulating agents, or ESAs, for the last 30 years, we've been using recombinati erythropoietin.

Finally, there's a drug that works a little bit differently, and this drug – the pathway for which the drug was created – actually won the Nobel Prize in 2019, so it's a very exciting, novel pathways for us. And so the way that these drugs work is 2 things. One is they actually induce endogenous production, which is your own production, of erythropoietin rather than giving exogenous, or outside, hormones. So it actually signals the body to increase genetic production of the erythropoietin in your own body, and that's number 1. Number 2, it actually can decrease levels of hepcidin, which as we mentioned in Chapter 2, hepcidin is the hormone that controls the iron that is upregulated in patients with kidney disease, and so by, one, increasing production of your own erythropoietin and, two, decreasing the hepcidin, which is the inflammatory blocker of iron utilization, these drugs really represent a very novel pathway that seems to be really ideal for our patients with anemia of chronic kidney disease. And then on top of all of that is, actually, these are oral medications, which makes it much easier for our patients, particularly those who are not on dialysis, who really aren't used to getting poked and prodded quite as often.

Dr. Vega:
Yeah, I agree. And so it seems almost that it fits into a more natural role in terms of the body's physiology. Reducing hepcidin levels, which are unfortunately elevated in CKD, better use of the iron that is available so the iron that we have been giving our patients for lo these many years could be used more efficiently and so therefore – and then, an oral treatment that fits much better into patients' and their supporters' lifestyle. It should be a lot easier to take and reduces patient burden, which will increase adherence. And because we have a relatively easier way to treat anemia in CKD, more folks will screen for it. So it really addresses a lot of the issues we talked about in Chapters 1 and 2. But there's always a balance.

Can you talk about some of the clinical trials of the HIF-PHIs and what they've shown in terms of efficacy as well as tolerability and safety?

Dr. Raghavan:
Yeah, absolutely. I think, as you point out, that there is always a balance, and of course, when you do these trials, you want to do 2 things. One, of course, you want to know efficacy – whether these drugs actually work. Do they raise the hemoglobin? Do they treat the anemia? That's what, of course, we want them to do. And second, what is the risk factor for these trials, meaning what is the potential harms, and how can these be mitigated, and exactly what's causing these harms? And so I'll focus, really, on 3 trials. And before I do that, I do want to mention there are 3 drugs in these pathways. And so they all end with the word "stat," but there's roxadustat, vadadustat, and daprodustat, and these are the 3 drugs that I'll be talking about within this pathway. And so the trials that were done, the first trial I'll mention is in non-dialysis patients, and again, this is patients with chronic kidney disease stage 3, 4, 5, and of course patients with anemia of chronic kidney disease.

And the OLYMPUS trial studied roxadustat and basically compared roxadustat to a placebo, and it was mainly an efficacious trial to see whether the medication actually raised the hemoglobin. And what they found was that, not surprisingly, the medication works. It does raise the hemoglobin to the prespecified threshold of 10-11.5, as we mentioned.

The next trial that I'll talk about is the PROTECT trial, which used vadadustat. And this trial is really important for us nephrologists in the treatment of anemia of chronic kidney disease because this trial was a non-inferiority trial that did not compare the medication to placebo, but rather compared to standard of care, which is recombinant erythropoietin. And so not surprisingly, the drug worked just as well, it was a non-inferiority trial, which showed that the drug was as efficacious as recombinant erythropoietin. But unfortunately, the study did show that there were some increases in cardiovascular events, which you know, led to some increase in mortality among patients, and this was statistically significant, leading the FDA to reject vadadustat for approval in the United States.

In the third trial or the ASCEND trial – so the ASCEND trials used the medication daprodustat. Daprodustat is the third of the "stat" drugs that we're talking about. And the ASCEND trials were done. There were several ASCEND trials, but ASCEND-D was done in dialysis patients, and ASCEND-ND was done in non-dialysis patients. Similar to the previous trials, this drug, daprodustat was compared to standard of care, which is recombinant erythropoietin, and basically to see whether – it was a non-inferiority trial – to see, one, whether the hemoglobin was raised to the prespecified target of 10-11.5 and, two, to make sure that there was no increase in cardiovascular events, which, of course, is the primary endpoint for this trial. The really wonderful news for us as nephrologists is the trial did meet the prespecified endpoint, and secondly, there was no increase in cardiovascular events compared to the standard of care, which is recombinant erythropoietin. So really a great win for all of us. The study did show, however, that daprodustat did have a signal that pointed towards increase in malignancies, particularly gastrointestinal malignancies, and this is something that is being looked at a little bit more closely by investigators from this trial as well as from the FDA prior to getting approval. This class of drugs are generally safe, and they are efficacious, and I think once we get a little bit more data about this increased signal of malignancies, then we'll hopefully be able to get some outcome data from the FDA regarding approval in the United States.

Dr. Vega:
Well, Rajeev, I know you have lamented the fact that you have not had as many advances in the field of nephrology as, say, cardiology. I've heard you describe that in a humorous way, but I can say, this is yet another win for nephrology here, and they're just kind of piling up. Y'all are on a roll, and that's great because, again, this is something that can certainly help patients. Because I agree – the general takeaway that I had from the trials was they do work.

They certainly do increase hemoglobin, and they put it in that, you know average – what I've seen from trials, maybe a couple points increase, in terms of grams per deciliter of hemoglobin, and puts it at a nice sweet spot between 10 and 11 where patients are going to feel better. And they're taking an oral drug, you know, which doesn't have a lot of significant tolerability issues, but, you know, there's those safety issues that have to be scrutinized as well. And so yeah, that – and especially in a group with CKD, that's a risk for cardiovascular events. You know, I understand why that was an important outcome of these trials. But daprodustat, you know, seems to have that non-inferiority compared with the ESAs that we commonly use. And so this is something that we hopefully can take heart in and then continue to examine it, you know, in terms of these clinical trials to make sure that we're not missing any other safety signals that could potentially harm patients in the future. But I think we're very hopeful about these agents and daprodustat in particular at this point.

Dr. Raghavan:
And I will say, you know, these drugs have been used in other countries, namely in Asia and Japan, China, for a little bit longer. I mean, they've been approved and in use, so we are expected to see more data come out. You know, we do have our annual conference coming up and so, definitely, we maybe expect to see a little bit more long-term data, which definitely will give us a little bit more comfort and hopefully will allay any fears about using the new medication, which of course is always going to be there with any new medication.

Dr. Vega:

And I think I want to make it perfectly clear to everyone watching that these agents are not FDA-approved. While they have been used in Asia for a longer period of time, they are not available in America yet. And so it's an exciting space to watch. It is a great advance, you know, regardless, in terms of the pathophysiology of anemia and being able to do something about it in a way that's, I think, not only response to the science, but also response to patients and their needs and could offer a real great option for individuals suffering anemia in CKD.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank you, Dr. Rajeev Raghavan, for joining me and for sharing all your valuable insights. It was great speaking with you today.

Dr. Raghavan:
Yeah, appreciate it. Thank you for having me, Dr. Vega.

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