Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/cme/directed-relief-in-ckd-ap-linking-targeted-therapy-to-clinical-outcomes/14967/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Directed Relief in CKD-aP: Linking Targeted Therapy to Clinical Outcomes

Announcer:
Welcome to CME on ReachMD. This episode is part of the Global Kidney Academy and is brought to you by Medtelligence.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Krüger:
Chronic kidney disease-associated pruritus, or CKD-aP, is an underdiagnosed condition that has significant negative impacts on the quality of life of patients with CKD, particularly those on hemodialysis. Today, we'll look at some cases that will shed light on the latest advances and targeted CKD-aP therapies, and their potential to provide much-needed itch relief and improve clinical outcomes for our patients.

This is CME on ReachMD, and I'm Dr. Thilo Krüger.

Dr. Fishbane:
Hi, I'm Dr. Steven Fishbane.

Dr. Manenti:
And I'm Dr. Lucio Manenti.

Dr. Krüger:
We have lots to discuss today, so let's begin. Lucio, I know you have a case that you'd like to share with us to kick off the discussion.

Dr. Manenti:
Yes, it is. I treated the patient, 50-year-old man. He started hemodialysis 5 years ago, and he started suffering itch – very dramatic itch with scratching lesions, and he cannot make a chore because itch was terrible, and he had very depressive condition after this period. More than 6 months with this problem, and we can't resolve it.

Dr. Fishbane:
Lucio, I'm wondering, the diagnosis can sometimes be tricky, with different causes of itching. How did you confirm that the patient was suffering from CKD-associated pruritus?

Dr. Manenti:
Oh, yes. First of all, he was suffering of CKD, because it is the pre-question for the diagnosis of CKD-aP. And he was suffering itch by more than 6 months, and he didn't show the signs of a dermatological problem, other than scratching lesions, and he was well dialyzed. He had well-controlled calcium and phosphorus product. And we counted, also, his blood in the office and total IgE antibodies were all normal, negative. And so we can be quite sure that this is a CKD-aP, the diagnosis. And we used the also the worst itch scale to evaluate the intensity of itch. And the sleep quality scale to evaluate the quality of sleep.

He tested 10 for the worst itch rating numerical scale, and 3 – that is one of the worst point for a sleep quality scale.

Dr. Fishbane:
That's a very thoughtful evaluation, and I think you very clearly defined what was happening with the patient. I've been very surprised over the years to recognize just how many patients suffer with CKD-associated pruritus. I think it's underappreciated. It's a common problem in our patients, and it's quite different than the normal itch that we suffer from, from time to time. I mean, it really has important

effects on patients' lives, on the way patients live, and I'm really glad that I've come to understand better how frequent it is. I'm wondering if you can walk us through your management. What was your approach for the patient?

Dr. Manenti:
With that, we approved starting with gabapentin at an increasing dose, without any beneficial effect. And gabapentin or pregabalin are often efficacious, and we have a number of more studies that confirm efficacy of them on CKD-aP. But however, the study size is very small, and we know – all the nephrologists know the risks of using these gabapentinoids in dialysis patients because we have the risks of dizziness falls, fractures, and so on. And these studies that showed effects, efficacy, didn't evaluate it – because the number size was too small – didn't evaluate these problems in the patient. So we had the opportunity to introduce the difelikefalin [DFK] as a treatment, and we evaluated the response using the scales, the worst itch itching scale, as I said previously, the sleep quality scale, and also the 5-D itch scale. And to evaluate the answer to the treatment, look to gabapentin before, and then to difelikefalin. And we used the standard dose you studied in your previous published work of 0.5 mcg/kg after every dialysis. And surprisingly for me, we had a complete response after only 2, 3 administrations of the drug. The scale's gone to 0, the [worst itch] rating scale, and the sleep quality scale ameliorated dramatically. So the patient remained responsive to the treatment for 6 months. And thereafter we tried to stop difelikefalin, but the itch returned after 4 weeks, and we restarted the treatment, and the treatment obtained the same answer, the same response to the treatment.

Dr. Fishbane:
That's very interesting, and I think it's so gratifying to be able to help somebody when they're suffering on a regular basis from symptoms like this. I'm wondering, Dr. Krüger, what's your perspective? How do you look at a case like this?

Dr. Krüger:
I think it's a very typical way how you approached and treated the patient, and I think it's also worth to mention that difelikefalin has not such side effects that we see from gabapentinoids, and what I often do in educating the patient, that DFK does not cross the blood-brain barrier due to its hydrophilic properties, and therefore this relieves the patient also to accept this new sort of treatment.

I think one thing that I would love to mention here – what we haven't discussed yet is that there is no clear evidence that phosphorus levels, PTH levels, are really directly linked to itch and the severity of CKD-aP. And I see it so often when I refer patients to the dermatologist with some itch. They are just returned with the commentary, "You just have to dialyze them better and bring phosphorus level down." So there is data out that clearly indicate that the severity does not correlate with PTH and phosphorus levels.

Dr. Manenti:
I agree.

Dr. Fishbane:
Yeah, I think that's really important. You know, we've certainly come to understand the pathobiology better in terms of itching in recent years. I think that there's a general acceptance and understanding that throughout the skin, there are nerve endings that are specifically for the detection of itch, but the signal of itch, as we go from nerve endings in the skin back to the spinal cord and the brain, it's not just a pure signal. It's modified, and one of the things that's very important as itch is signaled from the skin, is that opioid receptors – so the classic mu- and kappa-opioid receptors – are very important in terms of modifying the information that ultimately reaches the brain. And one of the things is that mu-opioid receptors – so we know these from treatment, for example, with opioid drugs – they typically cause itch, and mu-opioid receptors absolutely have a positive effect on promoting the signal of itch back to the brain. Kappa-opioid receptors have the opposite effect. They diminish the signal, and like many things in the body, there is a balance that's established and works wonderfully under normal conditions.

But unfortunately, for people that have kidney disease, there's a really striking imbalance, that mu receptors that promote itch are increased in our patients, whereas kappa-opioid receptors tend to be decreased. And this creates a problem, and it helps to explain why our patients suffer from itch, not only with such great frequency, but with such greater intensity than people often do. So I'm fascinated by the fact that difelikefalin specifically addresses this issue, and it does so through the kappa-opioid receptor. The receptor may be decreased by acting as an agonist at this receptor. It has specific effects in terms of reducing the signal of itch that have been tested in clinical trials.

So I'd like to hear a little bit more. Thilo, can you tell us more about your experience in treating patients with CKD-associated pruritus, and do you have a case that you might be willing to discuss?

Dr. Krüger:
Yes, sure. So as well, I had a 57-year-old woman with chronic kidney disease, and she was on hemodialysis since 3 years, and she did not mention her itch to us, so not me, not my colleagues, not our nurses. So only after active questioning from us – "Do you have issues,

like itching, and so do you suffer from this?" – then she admitted, "Oh, yes, and this is something that's bothering quite a lot." Also the physical examination then, after the review of some scratch marks, but they were more on the back, so this was not something that you see on your regular ward rounds. And only after this active questioning for this issue revealed this. So her blood parameters were not that fine, as Lucio's case, so the phosphorus was somehow elevated, as we see this frequently in hemodialysis patients. However, the PTH was very well controlled, with 62 mcg/L at the beginning of when we learned about that disease from her. We, indeed, started at the beginning with antihistamines. By the way, something which I today would not really start anymore with, but you learn by the way, and at the times we started with that. But it also did not work with this lady. And after that, we learned about this DFK program, and we were able to start also DFK in that lady. And yeah, to our and also our patient's surprise, after only 2 weeks of treatment, so you know, you give this after each dialysis, so some 5-6 administrations, the symptoms were dramatically reduced, and after 2 further weeks, or 4 weeks of treatments, they were almost gone or so well tolerated that the patient wasn't concerned about that anymore. And since then, she is on that therapy. She's very happy, does not feel any side effects, and we learned about that, and so appreciate the DFK and that sort of treatment, indeed, quite a lot.

Dr. Fishbane:
And when you consider the fact that there is the potential for sedation, for fatigue, for other related potential problems from these drugs, I really don't think that there is a place anymore for antihistamines in the treatments of these patients.

Dr. Krüger:
Exactly, Steven. I think that's a very good point, and there is also animal data out that has proven that the CKD-associated itch is not transferred by the histaminergic way. As you correctly said, it's the opioid pathway that is relevant here.

So to come to what I consider important to manage your patient with CKD-associated pruritus, and this is what you also described, Lucio, is to check what was first. To look for skin marks or to ask also the patient, "What was first? Did you have skin marks like blisters, nodules, some reddening of the skin before and then it started to itch?" Then I would clearly recommend to refer that kind of patient to the dermatologist, because it's very likely that this is a dermatological issue here. We also said that you tried emollients, which is a very good idea because it's an easy way to support the patient. It can relieve the itch, and it has virtually also not any side effects, so that is very clear. And as I said, I would skip antihistamines, and meanwhile, also gabapentinoids, despite it is sometimes helpful, but I would not really take the risk of these unwanted side effects here.

Regarding the quality of life, we clearly see that patients are sometimes dramatically impaired before we start an efficacious treatment of CKD-associated pruritus. With DFK, I have not really seen issues during the treatments. So the patients tolerated that very well, and as you reported, and also my case reported, after a few weeks of treatment, we see an improvement in CKD-associated pruritus here.

For the start of DFK, it's important to also assess the severity of pruritus, and as you already mentioned, this worst itch numeral rating scale, which I consider is a very easy tool to assess, first, whether there is pruritus at all, and then, with the same situation, you also can assess the severity. And if there is at least some moderate expression of itch, you fulfill the indication to administer difelikefalin, and therefore it's really open to start that treatment in these sort of patients.

For those just tuning, you're listening to CME on ReachMD. I'm Dr. Thilo Krüger, and here with me today are Dr. Steven Fishbane and Dr. Lucio Manenti. We are discussing new directions for the clinical management of moderate to severe CKD-associated pruritus, and how to improve the lives of our patients.

Dr. Fishbane, do you have further commentaries on the approval trials of difelikefalin?

Dr. Fishbane:
So I've been involved with research with different agents to treat itching, pruritus in our patient population and frankly, have been serially disappointed by drugs that we had studied and, in some cases, published on. So I was very excited at the end of the phase 2 program for difelikefalin, or DFK. Difelikefalin in the phase 2 program was demonstrably effective in terms of reducing itch, and that led me to have a great sense of anticipation as the drug moved into phase 3 studies. So the pivotal phase 3 studies for approval of difelikefalin were called the KALM-1 and KALM-2 studies. And in these studies, what we found was very gratifying. We found that in classic, placebo-controlled, randomized controlled trials, that compared to placebo, the efficacy for reducing itch with difelikefalin was very clearly demonstrated. So the drug worked. It worked effectively, and the time course of efficacy, I think, was important, that within the first 2-4 weeks of treatment, patients experienced very significant improvement. And I would like to point out that that was improved and sustained improvement over the course of time. So patients had consistent benefit in terms of reducing the troubling symptoms. But for me, it became even more interesting, that the effect of reducing itch in these patients – and I think this teaches us, as providers of care, something very important. Again, when we think of itch, we can sometimes minimize it based on our own experience, but when we consider patients with CKD-associated pruritus, it is just different. It has a greater effect, and it impacts aspects of life, like sleep and

social functioning. And indeed, in these studies, we went beyond evaluation of itch and looked towards how itch affected parameters of quality of life. And there, in KALM-1 and KALM-2, and in subsequent analysis, we're very happy to find that patients not only found relief from itch, but also found improvement in terms of overall quality of life. Life experience was improved in patients, and that includes various parameters that I found, for me, just particularly important. I think sleep quality is very, very important, so I was looking there. I was looking carefully, and very happy to see that patients treated with difelikefalin compared to placebo had improvement – so not only different parameters of quality of life, but sleep quality itself improved in patients. So I was really quite happy to see the results.

Dr. Krüger:
Thank you, Steven. I think very good points, and for me, 2 things were quite important are necessary to mention. It's very much appreciated that we see a very large trial, the first trial that assessed CKD-associated pruritus in that large trial population. So the other trials that have assessed other compounds like antihistamines, gabapentinoids, and others were only a few dozen patients large. So here, we have several hundreds, and I think this is also really a robust data set that we see.

And what also was a little bit puzzling to me is that we, of course, do have some substantial placebo effects, which is probably not surprising, but despite that, difelikefalin was statistically significantly better than the placebo group. So what we see in the effect with DFK is not only the placebo effect, so it really works, also, in this area, and it also fulfills this mode of action that was postulated in the generation of CKD-associated pruritus.

Well, Steven, based on the clinical trial data that we just discussed, are you integrating kappa-opioid receptor agonists now into your treatment plans?

Dr. Fishbane:
Yeah, I am. And you know, here, I think it becomes really interesting to discuss practical aspects of care. I want to remind everybody that this is an injected treatment, so for hemodialysis patients, the drug is administered not just during the treatment, but very specifically at the end of the dialysis treatment. And with that therapy, we get sustained efficacy that lasts over the period – not only up until the next treatment, but we start to get this repeating effect, where patients get relief from pruritus over the course of time.

Definitely noted some factors that I think are important. The first – and this is so critically important – is that patients did not necessarily come to us to talk about itch. There have been studies of this subject, and we realize from these studies 2 things that I think are critically important. One, really substantial number of our patients suffer from itch. The frequency is quite high, and in some patients it may be a more minor issue, and treatment with emollients may be effective. In other patients, it's more severe. But we certainly have learned the lesson that if we don't ask patients, the patients feel a certain sense of uncertainty in terms of who do you speak to? Who do you bring this complaint to? And in studies, some have mentioned it to nurses, some to their primary care physicians. But nephrologists only 24% of the time are told by the patients about itch. Well, that makes clear to me that part of the discussion with patients is specifically asking, "Have you had itch as a problem? Do you suffer from itch?"

And I think as we try to take a more holistic approach to thinking about patients and moving beyond very important factors like adequacy of dialysis, anemia, bone and mineral disease, thinking about symptoms more broadly. And I would say that itch specifically, because of our ability now to effectively treat it, has been important. Now, for some people, this may be achievable best simply by talking to the patient, whether in interdisciplinary settings or with a physician speaking with the patient directly. "How are you feeling? Have you had problems with itch since I saw you last?" In other cases, it might be beneficial to use more systematically certain scales that have been developed, and there's many of them. It turns out that the Worst Intensity Numerical Rating Scale, or the WINS scale – it's a very simple, 0-10 scale, that the patient simply marks over the last period of time, what has been the overall intensity of their itching. It's a very easy way to look at how much itching the patients experience. I will say from my experience, I talk to the patient and I ask about their itching, but if you want to understand more systematically in your, for example, dialysis facility, using scales like this can be a very effective way to be able to find patients that have itching.

Now, we also want to think about difelikefalin treatment. So with the approval of the drug, it's been very gratifying. Phase 3, there are placebo-controlled studies, but it was very clear to me that patients were benefitting. Now in clinical practice, I see it regularly; I see it repeated. Patients that are unable to address the itching that they're having – talk to them about it, initiate therapy, and then the consideration is when do you discontinue treatment? I often give at least 3 months to make sure all of the patient's itch is better. I'll try to discontinue treatment after 3-6 months. In some cases, we can do so. In some cases, we have to reinitiate treatment. I often find that I have patients that are calling out to me in the dialysis facility and reminding me that the itch has come back and the patient needs to be treated again. I think, from the standpoint of the providing physician, it's simply using clinical judgment, this is what we do, in terms of understanding the necessity to continue with treatment.

Dr. Krüger:

May I ask the question to you, Steven or Lucio, is there any patient who should not be treated with difelikefalin? Is there any limitations that we see where should we be cautious in using this, or is this a rather easy approach?

Dr. Fishbane:
Thank you, that's such a good question. In most of my patients, there hasn't really been a need for that much selection. But there is 1 thing that I think is helpful from a clinical standpoint, and where I have some concern is in the older, more debilitated patient. And in our dialysis facilities, we do have a few patients that fit this kind of characteristic. It's the older patient with some cognitive issues.

I think their treatment with most drugs, we should be very careful about, and I think that these are the patients where particular care with drugs, like difelikefalin, that can have certain side effects that could be problematic would be used with care. We need to consider; we need to think about how we would approach such patients.

Dr. Manenti:
Yes, I think the same, Dr. Fishbane.

Dr. Krüger:
Yes, absolutely. Thank you very much. I think these are really important issues and points that we heard that we learned of.

May I ask you to boil it down on a 1 key take-home message? Maybe to start with you, Lucio.

Dr. Manenti:
The more important question is to listen to the patient and understand the problem, because in the past, nephrologists under evaluate this question, and it impacts on quality of life and mortality.

Dr. Fishbane:
Yeah, thank you. Sure. I guess, 3 very quick things. One – just, again, amplifying the importance that patients don't like to talk about it; they don't bring it up. It's so valuable and so easy for us in practice to be able to ask patients, "Do you have itching? Is it a problem? Second, again, I just want to review the fact that it's so fascinating that we've learned about the importance of the opioid receptors in terms of itch sensation and what an important role they play in our patient population. Third, again, difelikefalin, which works specifically on that problem in terms of the kappa-opioid receptor, and I kind of get a special joy out of the fact that it works specifically at where the problem is from the standpoint of pathobiology. So attentiveness to patients and treatment where appropriate by the means that are necessary for the specific patient.

Dr. Krüger:
Well, I consider the multidisciplinary approach very important, so there needs to be a collaboration among nephrologists, dermatologists, and potentially also other healthcare professionals like the GPs, also the nurses, for example. And therefore it's really good to see that, for example, in Germany, difelikefalin has now made it into a national guideline, which is a dermatological guideline, at least mentioning that DFK has fulfilled the pivotal trial, the phase 3 program, and is underway of approval in Germany, and this is where we are now. In addition to this, also in the UK, the NICE [National Institute for Healthcare and Excellence] guidelines also have been adapted in order to recommend DFK as sort of a treatment in patients with CKD-associated pruritus.

Well, that's all the time we have today, so I want to thank our audience for listening and thank you both, Dr. Steven Fishbane and Dr. Lucio Manenti, for joining me and for sharing all of your valuable insights and expertise. It was really great speaking to you today. Thank you.

Dr. Fishbane:
It's been such a great pleasure to be part of this program. Thank you so much.

Dr. Manenti:
Thank you and goodbye.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Medtelligence.

To receive your free CME credit, or to download this activity, go to ReachMD.com/Medtelligence. Thank you for listening.