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Real-World Cases: The Itch Clinic: Treatment of Chronic Kidney Disease-Associated Pruritus in Hemodialysis Patients

Announcer:
Welcome to CME on ReachMD. This replay of a live broadcast is titled, “The Itch Clinic: Treatment of Chronic Kidney Disease-Associated Pruritus in Hemodialysis Patients – Real World Cases,” which is provided by AKH – Advancing Knowledge in Healthcare – and is supported by an educational grant from Vifor Pharma, Inc. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Chronic Kidney Disease-Associated Pruritus, or CKDAP, is believed to affect one in four patients with CKD, up to 86% of patients on dialysis, and approximately 37% of patients with ESKD report moderate to extreme itching. Pruritus has a substantial impact on quality of life, but it remains underdiagnosed and undertreated. Through the use of two real-world cases, we will examine diagnosis and management of CKDAP, including the recent approval of the first targeted treatment for this common, yet consequential, complaint. I’m your host, Dr. Jennifer Caudle, and I’d like to welcome Dr. Steven Fishbane and Dr. Shayan Shirazian to the program this evening, who are joining me to discuss real-world cases of patients with chronic kidney disease-associated pruritus. Dr. Fishbane and Dr. Shirazian, welcome to the program, and thank you so much for being here today.

Dr. Fishbane:
Thank you, Dr. Caudle. Great pleasure to be part of this.

Dr. Shirazian:
Thank you for having me.

Dr. Caudle:
Well, I’m excited to have both of you here. This is going to be a great program. Before we get started, I’d like to remind the audience that there will be a polling question, and actually a couple of polling questions throughout this presentation. To participate, please take out your phone and text “reachmd” to 22333, and then as each question appears, you can text your answer using the corresponding letter. Additionally, at the end of this live broadcast, we will be taking audience questions during our live Q&A. To submit questions during the presentation, please type them into the chat control panel on your left, or via Facebook Live. We will try to answer as many questions as we can during our time allotted. So, we’re going to begin now with Dr. Shirazian. Dr. Shirazian, can you start us off with an overview of the epidemiology of pruritus in the CKD patient population, and how you might evaluate patients with CKD for pruritis?

Dr. Shirazian:
Sure, I can do that. So, as we’ve alluded to, chronic kidney disease-associated pruritus is common. It’s been estimated that it affects 25% of patients with pre-dialysis chronic kidney disease, and between 50-86% of patients on dialysis. Retrospective studies have shown that over 50% of dialysis patients have at least mild pruritus, and 8-10% have the severe to very severe itching. A retrospective analysis of the dialysis outcomes and practice pattern survey database has shown that 37% of patients on dialysis have moderate to extreme itching. So besides being a nuisance, CKDAP can have serious clinical consequences. It has been associated with insomnia, chronic fatigue, discomfort, social isolation, anxiety, depression, and it negatively impacts quality of life. Dialysis patients have been shown to have a substantial impact on their quality of life and quality of sleep when they itch, and non-dialysis CKD patients with pruritis have lower quality of life scores, depression symptoms, and have restless sleep.

There is not one particular profile that characterizes a patient with CKDAP, and the presentation is variable. Patients will often report itching in the back, torso, head, neck, and shunt arm, and the itching has been shown to be exacerbated by extreme hot or cold, stress, physical activity, and showering.

So when we assess patients for CKDAP, the first step is to make sure that they're meeting National Kidney Foundation guidelines for dialysis efficiency, and mineral and bone disease management. So we check the serum parathyroid hormone, and if it's above our target, we try to treat to target. If the calcium and phosphorus levels are elevated, we try to normalize those levels, and we try to target a dialysis clearance of over 1.2. When evaluating the itching, it's important to do a good history and physical, in terms of getting the frequency, severity, location and impact of the itching. We also assess for dry skin, and we treat that when applicable because treating dry skin has been shown to mitigate but not completely, remove itching in patients with CKDAP. And because CKDAP is so common in patients on dialysis, we consider any itching in this population to be related to CKDAP, unless there's a clear alternative explanation like a comorbid skin or a liver condition.

Assessing for CKDAP involves several scales that rate the severity and impact of CKDAP. These include the dermatology QOL index, the Skindex and the 5-D pruritus. There are also scales that just assess the degree of itching and these include the visual analog scale, shown there at the right, the numeric rating scale, the verbal rating scale, and the kidney disease quality of life short form, or KDQOLSF.

Dr. Caudle:
Thank you, Dr. Shirazian. And now, Dr. Fishbane, can you introduce us to your patient case?

Dr. Fishbane:
Yeah, pleasure. So, this is a patient who I took care of, and I think this patient is fairly indicative. It's a 53-year-old patient. She's with end stage kidney disease, on dialysis three times per week for the past three years, because of end stage renal disease with membranous nephropathy. She's generally doing well, but mentioned to her dietitian, during discussion of monthly labs, that she's had itching that's been worsening over the past three months.

Now, in trying to understand better how this was affecting her, it was clear that the itching was present at every dialysis treatment, and it was exacerbated after physical activity or showering. When attempting to quantitate with a survey tool, the dietitian found on the numeric rating scale, a score of seven to eight, and this indicates severe pruritus. The impact on the patient went well beyond just itching. She noted that it affected her during the nighttime, interfering with sleep, and in fact, the previous night, it had taken her almost two hours to fall asleep due to itching. This was mostly over the legs and her torso.

Dr. Caudle:
Thank you so much for that, Dr. Fishbane. And now, this brings us to our first polling question. If you've not done so already, please text "reachmd" to 22333. As each question comes up, you can take a moment to, text in your answer using the corresponding letter. And now on to our audience question number one: So, how confident are you in your understanding of how current treatments address the theories regarding the pathophysiology of CKD pruritus? Are you very confident –letter A; B – moderately confident; C – minimally confident; or D – not confident at all. We will give just a second for our respondents to weigh in here. I do see the majority feel moderately confident, some feel minimally confident. And of course, we hope that, your confidence does increase as the program continues. Thank you for that.

Now as we continue, Dr. Fishbane, I'd like to come back to you. Can you explain how the current theories regarding our understanding of the pathophysiology translate into therapies? And how do you apply these theories to management selection for your patient case?

Dr. Fishbane:
So we have to accept the fact that we do not fully understand what the cause of pruritus is completely, but we are generating a pretty good understanding, and it's helpful to categorize into four broad groups. One would be toxin deposition – so imagine with uremic toxins circulating in the blood stream and depositing in skin and peripheral nerves, we can imagine the effect that this could have on local tissue, with irritation and in the skin, the production of pruritus.

Peripheral neuropathy – so itch is, certainly transmitted via the nerves. The peripheral nerves here are being critically important, and when you have a patient who has peripheral neuropathy, it's reasonable to consider that the itch might have the same pathophysiology. In those cases, gabapentin or pregabalin – drugs aimed at neuropathy – could be effective.

Immune system dysregulation – so the immune system certainly plays an important effect in terms of mediating the degree to which signals are transduced, in which, pain, discomfort and itching could be experienced. And I think a really interesting area is in opioid dysregulation. So, this has been studied with difelikefalin, a drug you'll hear more about. It's a peripheral kappa opioid receptor agonist, and this was recently approved, and it helps us to understand better that the opioid system itself and its receptors might be important in terms of itch.

In this patient, we had approached her, treated her with antihistamines, and encouraged her to focus on taking the prescribed phosphate binders. After speaking to her over time, it was just becoming clearer that we were not making progress. There wasn't a significant change in her symptoms.

We looked at her laboratories, and we saw here that in terms of the bone mineral access – calcium, phosphorus and parathyroid hormone – over the course of a couple of months, the calcium concentration, phosphorus and parathyroid hormone were generally in the target range, and not really indicating a potential cause of pruritus. In terms of dialysis adequacy, we saw that the kt/v, two months prior and currently, were certainly within the range of adequacy – not suggestive at all that they might be contributing to the patient's pruritus.

As we think about a systematic approach to the evaluation of pruritus, I think it's good to consider – the way we do all medicine – history, physical examination, synthesis of data. In history, I'm really interested in the extent of itching. The duration – how long has it been present, and is it present at dialysis or more frequently? The parts of the body that are affected. On physical exam, the focus is clearly on the skin. Are there areas that indicate potential skin disease? Are there excoriations that are indicating to us that the patient's been scratching excessively? And on biochemistry, as we've discussed, looking at the mineral access, considering dialysis adequacy. Now there's certainly gonna be cases where patients have skin diseases like anybody else can get, and in non-uremic pruritus, we might work with a dermatologist, in order to better understand the patient's condition. But, most cases of pruritus that we see will turn out to be uremic pruritus. And we need to try to understand better in individual patients what might be going on. Especially in the winter months, with the use of heat, we find that there's a lot of dryness of the skin, and in those cases, the use of good quality moisturizers, or changing soaps, changing shampoos could be helpful and really improve skin quality.

If we're concerned about toxin deposition, then we're thinking about the quality of dialysis and assessing for adequacy. With peripheral neuropathy in my patients who have numbness, pins and needles sensation or nighttime pain, maybe they're already taking medicines like gabapentin. I'm considering the possibility that those patients' itch might also be related to peripheral neuropathy, and their – a drug like gabapentin or pregabalin might be, beneficial. If it appears to be immune system dysregulation, we might treat with antihistamines, and in fact, UV light therapy can have effects on modulating the immune system. It can be cumbersome, and you know, I think this often limits therapy. And then we get to opioid dysregulation, and this is where the agent difelikefalin has been found to be effective. But you know, the truth is, as you'll see in the studies, that difelikefalin's been tested in patients on dialysis with pruritus of all causes, and it really is an effective medication after you've gone through the initial evaluation and conservative therapy, to be able to effectively treat patients with pruritus.

So, when we come back to our patient, we ended up starting her on gabapentin, initially 200 milligrams at the end of the dialysis treatment. We started to increase the dose, to try to get some effectiveness, but the patient developed unsteadiness with walking. And I guess this has been my experience, that we find a relatively narrow therapeutic window that – we get a little too close to toxicity with effectiveness, with gabapentin. Patient continued to suffer for itching. This went on over months, and, happily, she did receive a kidney transplant. At that point, there was significant, improvement in terms of her itching.

Dr. Shirazian:
Steve, great case. I wanted to ask a question about it. It seemed like there was some dissatisfaction with the medications you used to treat the pruritus, the antihistamines and the gabapentin. Was there any consideration to trying difelikefalin in this patient?

Dr. Fishbane:
Yeah, Shayan, you're right, you know, this was frustrating, as the treatment of itch, I think, often used to be that we're using medications, not getting very far, the patient was frustrated, so dissatisfaction is a good word, I think, to describe the situation. Difelikefalin, I think, would have been a really nice option. Unfortunately, the treatment of this patient was prior to, the availability through the FDA in August of 2021. Thanks for the question.

Dr. Shirazian:
Thank you.

Dr. Caudle:
And thank you both for that discussion. Thank you, Dr. Fishbane, for that case. You know, Dr. Shirazian, we're gonna come back to you now. I know that you have a case to share with us as well. Can you provide some background on your patient, and the results of your evaluation?

Dr. Shirazian:
Yes, Dr. Caudle, I do have a case. So my case is of a 65-year-old woman with end stage renal disease due to diabetes mellitus, who's been on three times a week hemodialysis for the past five years. She recently switched to my dialysis shift from an earlier shift, in part due to nonadherence to her hemodialysis treatment. So for the past three months, she's been skipping treatments at least once a week,

and when she was, addressed by the social worker about this, she says that she really does not know why she's skipping. The social worker does note that her recent quality of life scores have been lower, and her primary nurse noted that she had itch marks at the site of her fistula.

So, I think it's important to stop here. You know, when providers are, addressed with the high prevalence of chronic kidney disease-associated pruritus in their patients, they're often shocked. And I think the reason for this is that patients are often underreporting this condition, because they feel like not a lot can be done to treat it, or they have other medical problems and they don't want to bother the nephrologist. It's also the providers that are often not asking about this condition because they feel like there're not great treatments or they just don't know about the treatments. So when you have a patient who has itching, who's on dialysis, it's really important that you ask directed questions like, "Are you having a problem with itching?" to really get at the root of the problem.

So back to our assessment. You know, when we addressed the patient on her monthly rounds – and this was multidisciplinary rounds, so it involved the social worker, the nurse, the nurse practitioner, all working as a team – she said she felt fine. She had no history of skin or liver conditions that could cause itch, but when you did the physical, you noted that she had excoriations on her arms, and partly excoriated, hyperpigmented nodules on her back – also known as prurigo nodularis – and patches of dry skin on both her arms and legs. No other rashes were noted. When you asked her directly about this itching, she did admit that she had severe, generalized itching, both before, during and after dialysis, that affected her mood, her sleep, and this is despite taking gabapentin at night for diabetic nephropathy.

So our initial management in this patient was to make sure she was adhering to KDIGO-defined goals for CKD-MBD management, and dialysis treatment and efficiency. We also wanted to comanage her dry skin, which as we said, may improve itching, and we did a routine set of labs.

So her labs three months prior, when she had itching, showed, calcium, phosphorus and PTH levels that were within target for our, guidelines for CKD-MBD management, and her dialysis clearance was good. She had a kt/v of over 1.2. Her current labs, though, showed that her phosphorus had gone up to 8.8, and her parathyroid hormone also went up to 1,260. Her clearance was still good.

Dr. Caudle:
Thank you so much for that, Dr. Shirazian. And now this brings us to our next polling question. Again, if you've not already done so, please text "reachmd" to 22333. As each question comes up, you can take a moment to text in your answer using the corresponding letter. So our audience question number two is this: What is your next step in treatment? A – provide reassurance, encourage adherence to dialysis and no further treatment; B – increase phosphorus binders and no further treatment; C – recommend topical emollients and no further treatment; and D – encourage adherence to dialysis, increase phosphorus bind, and recommend topical emollients; if itching persists initiate difelikefalin. Alrighty, so let's see what our audience has said. It looks like most, have suggested, or said, item number D. Some say letter B. the actual answer is D – encourage adherence to dialysis, increase phosphorus bind, recommend topical emollients, and then initiate, difelikefalin if itching persists. Okay?

So as we move forward, Dr. Shirazian let's return to your case now. How did you treat your patient, and how did the case resolve?

Dr. Shirazian:
Okay. Yeah, so remember, in our patient, the phosphorus level had gone up, so our first step was to try to normalize the phosphorus level, and we increased her phosphorus binders. We also ensured that she was more adherent with dialysis, and going three times week, and we treated her eczema with topical emollients, like, ammonium lactate. The itching improved slightly, but it did not abate. And at this point, we considered difelikefalin, which is the newly-approved, peripheral kappa-opioid receptor agonist.

So just to tell you a little bit about difelikefalin, it's the first FDA-approved medication to treat moderate to severe itching in patients with CKDAP undergoing dialysis. It's a peripheral kappa-opioid receptor agonist, and it's administered three times a week, after dialysis. It reduces the activity of sensory nerves that relay itching from the skin to the spinal cord or brain. The adverse effects associated with its use are diarrhea, dizziness and vomiting. It's important to note that it's the new receptor that's associated with misuse and abuse, and euphoria and dysphoria – not the capital BR receptors, so it's not hitting the abuse pathway here.

So, some of the trials – so the KALM-1 study was published in the New England Journal in 2020, and Dr. Fishbane was the lead author. It involved 378 dialysis patients with moderate to severe uremic pruritus, who were randomized to 0.5 micrograms per kilogram of IV difelikefalin or placebo, three times a week for 12 weeks. And after 12 weeks, there was a significantly greater estimated percentage of patients in the difelikefalin versus placebo group – 49.1 versus 27.9% – with an improvement of greater than or equal to three points from baseline on the itching score, and there were also significant improvements in quality of life, mood and sleep.

The more recent study is the KALM-2, phase 3, international global study, with a 52-week follow-up period. It involved 473 hemodialysis patients, and again, after 12 weeks, there was a significantly greater estimated percentage of patients in the difelikefalin versus placebo

group – 52% versus 31% – with improvements of greater than or equal to three points from baseline on the mean worst itching intensity, NRS, score. There was also, at 12 weeks, a significantly greater estimated percentage of patients in the difelikefalin versus placebo group – 37% versus 18% – with improvements of greater than or equal to four points from baseline on the WI-NRS score.

So in our case, we did discuss difelikefalin with our patient. We discussed it as a team. Again, it was the dialysis nurse, it was the social worker, it was the nurse practitioner – and we all, with the patient, decided to initiate treatment. We administered 0.5 micrograms per kilogram of IV difelikefalin, three times a week, after dialysis, and the initiation resulted in the resolution of itching. And at four weeks post-difelikefalin initiation, the patient reported that she had a complete resolution of her itching. She also reported improvements in sleep and mood, and she was back to being completely with heren – adherent with dialysis, going three times a week.

Dr. Fishbane:
Shayan, this is, certainly an interesting case. Caught me by surprise. I thought when we first talked about this patient, that it was probably gonna be related, to noncompliance, to a patient, perhaps had not bought in to her dialysis prescription, but it looks like this was a real situation where the pruritus was just interfering with her ability to sit in the chair for the prescribed time. Is that what the team felt was primarily to do here?

Dr. Shirazian:
Yeah, I mean, that's a great point. So, you know, initially we just thought she was a non-compliant patient, but actually, when we really probed into it, we felt at the end that it was the itching, it was the CKDAP, that was causing her noncompliance because when we treated it, she went back to being completely compliant. So it really is important to probe in your patients, you know, what's affecting their quality of life, what's causing them to miss dialysis. It's a great point.

Dr. Caudle:
Hm. And thank you both for that discussion. Thank you, Dr. Fishbane, for your comments. Dr. Shirazian, thank you for the case. Dr. Fishbane, we're gonna come back to you as we near the conclusion of this program. You know, let me ask you, if there are any key take-home messages that you would like to share with our audience.

Dr. Fishbane:
Yeah, I sure would. So I think that we've discussed some really important considerations as we think about patients with CKD-associated pruritus. The first is it's really important that we stop and think about the fact that this is just a much more common problem than we've realized. It affects much more than just simple itching that we may have experienced, because in our patients, it really is more extensive and impacts on quality of life. We've seen that there are different factors that play a role in causing the pruritus, but we do have therapeutic agents that are available to treat, and most specifically, the FDA just recently approved the first targeted agent, difelikefalin, to manage patients with CKD-associated pruritus. We must remember, the only way we're gonna have the opportunity to help patients is if we understand and find out about their pruritus, so as we've heard a couple of times throughout tonight's program, always ask your patients about itch.

Dr. Caudle:
Well, thank you so much for those very important take-home messages, Dr. Fishbane. We will now transition to our live Q&A segment, where we're gonna hear questions from our live audience. We actually have a few questions that have come in, and, I'm taking a look to see what we have here. It looks like our first question from the audience is directed at Dr. Shirazian. So Dr. Shirazian, for how long will patients need to stay on difelikefalin? An excellent question.

Dr. Shirazian:
Yeah, that's a very good question. So you know, the initial studies were for 12 weeks, and you know, there has been a long-term follow-up – 52 weeks. It's really still unclear about how long they need to be maintained. I think that itch will probably kind of, peak and then kind of wane. I think that, at some point, you know, we will try to titrate them off the medication, but, you know, we're still trying to figure out how long they need to be maintained on this medication. There may have to be a taper-off period, but that is great question, and it's one of the things we are trying to determine at this point.

Dr. Caudle:
Hmm. Great, thank you so much, and it looks like we have time for just one more quick question. This one's going to be directed towards Dr. Fishbane. The question is, other than difelikefalin, what can we recommend to patients who aren't responding to traditional approaches?

Dr. Fishbane:
Right. So, look, I think that, as we've spoke about, the use of moisturizers, antihistamines, different types of approach – UV light therapy in rare cases where the patient's willing to put up with it. But we're not successful with conservative and traditional managements. I

think, difelikefalin is, particularly helpful, because we've just been frustrated, I think, frequently in the past with some of the agents that we've used, and thank you for the question.

Dr. Caudle:
Of course. Those were excellent questions from our audience. Thank you so much for submitting them and to our experts as well. This was a great way to round our discussion on chronic kidney disease-associated pruritus. I would like to officially thank my guests, Dr. Shayan Shirazian and Dr. Steven Fishbane, for helping us better understand the epidemiology and assessment of CKDAP, its pathophysiology as well, and the clinical trial data on a new treatment, through patient cases. Drs. Fishbane and Shirazian, you were excellent, and it was wonderful speaking with you today.

Dr. Fishbane:
Yeah, thank you so much. It's been a pleasure to be part of this program.

Dr. Shirazian:
Yeah, thank you very much. It was my pleasure as well.

Announcer:
Thank you for joining our live broadcast replay, titled, "The Itch Clinic: Treatment of Chronic Kidney Disease-Associated Pruritus in Hemodialysis Patients – Real World Cases." To receive your free CE credit, or to download this activity, go to ReachMD.com/cme. This is CME on ReachMD. Be part of the knowledge.