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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 Pruritis in Hemodialysis Patients, which is provided by AKH, Advancing Knowledge in Healthcare and is supported by an educational grant from Vifor Pharma Incorporated. 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, and up to 86% of patients on dialysis, and approximately 37% of patients with ESKD report moderate to extreme itching. Pruritus has substantial impact on quality of life, but it remains underdiagnosed and undertreated. Greater understanding of the potential pathophysiology has led to investigations into more targeted treatments 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. They are joining me to discuss chronic kidney disease-associated pruritis. Dr. Fishbane and Dr. Shirazian, welcome to the program, and thank you so much for being here today.

So before we get started, I'd like to remind the audience that there will be polling questions throughout this presentation. To participate, please take out your phone 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 and A. To submit questions during the presentation, make sure you 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 the time allotted. So let's begin.

Dr. Shirazian, can you start us off with an overview of the problem of pruritis in the CKD patient population and the consequences of CKD pruritis?

Dr. Shirazian:
Yeah, so the – so chronic kidney disease-associated pruritus is common, and it's estimated to affect approximately 25% of patients with pre-dialysis chronic kidney disease, and 50 to 86% of patients on dialysis. Studies have shown that over 50% of patients on dialysis have at least mild pruritis and 8 to 10% have severe or very severe itching.

A study of the dialysis outcomes and practice patterns survey database was consistent with this high prevalence with 37% of patients having moderate to extreme itching.

So besides being a nuisance, chronic kidney disease-associated practice also has clinical consequences. It's been shown to cause insomnia, chronic fatigue, discomfort, social isolation, anxiety, depression, and it negatively impacts quality of life. For dialysis patients, there's substantial effects of CKDAP on quality of life and sleep. And for non-dialysis CKD patients, it has been shown to affect quality of life scores, depression symptoms, and to cause restless sleep.

The presentation of CKDAP is variable. So itching is often reported on the back, torso, head, neck, and shunt arms. And it's been

reported to occur anytime in relation to dialysis, either before, during, or after. It's also exacerbated by extreme hot or cold, stress, physical activity, and showering.

So interestingly, nephrologists are often shocked about how high the prevalence of chronic kidney disease-associated pruritus is in their patients. And studies have shown that they dramatically underestimate the prevalence of this condition. And I think the reason for this is twofold. So it's probably that patients are underreporting the symptom because they feel like nothing can be done in terms of treatment for it. And also, physicians feel like also that nothing can be done for treatment. And they also underestimate the impact of this condition. So if you really want to know if your patients are having chronic kidney disease-associated pruritus, you need to ask directed questions about this problem. For example, are you having a problem with itching?

Dr. Caudle:
You know, that makes a lot of sense. And, you know, moving on and moving forward with that, how do you evaluate patients for pruritus and for possible causes of pruritus?

Dr. Shirazian:
Okay, yeah, so that's a very important question. So I don't think this all falls on the shoulder of the nephrologist. So dialysis patients often have a whole healthcare team that includes nurses, social workers, nutritionists. And these patients often see dialysis patients more than the nephrologist, often once a week. So getting everyone involved in the assessment of these patients is important.

Now the first step in the assessment of a patient with chronic kidney disease-associated pruritus is to make sure that they're meeting National Kidney Foundation guidelines for dialysis efficiency and for creating mineral bone disease. So if their serum parathyroid hormone level is high, treating that level to within goal range. If their calcium or phosphorus is out of range, again, trying to treat that to a normal range for a dialysis patient and what is in the guidelines by the National Kidney Foundation. And finally, if their clearance is less than 1.2, to try to bring their dialysis clearance above 1.2, to fall within guidelines of the National Kidney Foundation.

The second step is once you ensure that they're meeting these guidelines is to assess for dry skin, and if it's present, to treat it. So dry skin often co-occurs with chronic kidney disease-associated pruritus. And although it's not the cause, treating it can improve the symptoms but not completely abate the symptoms of chronic kidney disease-associated pruritus.

And finally, when you're assessing a patient for chronic kidney disease-associated pruritus, it's important to look for alternative conditions that may cause the symptoms of itching, like comorbid skin or liver conditions. But because of the high prevalence of CKDAP, one should assume that itching in this population is related to CKDAP, unless there's a clear alternative explanation for this.

In terms of rating scales, there are many. So there are several rating scales that look at the severity of chronic kidney disease-associated pruritus and its impact on quality of life. And these include the dermatology QoL index or the DLQI, the Skindex, and the 5D pruritus scale. There's also scales that just look at the severity of itching. And those include the visual analog scale shown there on the right, the numeric rating scale, the verbal rating scale, and the kidney disease quality of life short form, the KDQoLSF.

Dr. Caudle:
Excellent, thank you so much for that, Dr. Shirazian. And this brings us to our first polling question. We are interested to hear what you think and how you feel. If you have not done so already please text ReachMD- excuse me – to 22333. As each question comes up, you can take a moment to text in your answer using the corresponding letter.

This is question number one that you are seeing. The question is: How confident are you in your understanding of the current theories regarding the pathophysiology of CKD pruritus? A: Very confident; B: Moderately confident; C: Minimally confident; and D: Not confident at all. Let's take a moment to see how you feel and see, you know, see what's going on out there.

Okay, so we have a few people, a number of people that are feeling moderately confident and a few people feeling not at all confident. So you know, it sounds like that we're all in the right place. This is very helpful to know. We will continue to assess our knowledge as we move forward.

Okay. So as we move forward, rather, Dr. Fishbane, let's go to you for a moment. You know, I understand the pathophysiology of CKD-associated pruritis is not clear. And you tell us the current theories?

Dr. Fishbane:
Yeah, thank you, Dr. Caudle. So this is definitely an area that is an evolution. And we don't have a complete understanding. I mean, that's absolute, but there are theories. And this helps us I think a little bit in terms of how we look at our patients and gives us I think a foundation for thinking about the therapies that we might be using.

So the four primary theories that underlie the way that we think about pruritis. The first has to do with toxin deposition. So in our uremic

patients, might there be the deposition of specific uremic toxins that might be important in terms of affecting nerves - infecting - affecting the sensation and the potential experience for the patient of itching.

The second would be peripheral neuropathy. Now, we know that our patients have a lot of peripheral neuropathy. And we often think of that in terms of loss of sensation, or burning, pins and needles, but really good for us to remember that it also can cause the sensation of itching and damage to the nerves, especially the long nerves to the legs and arms, might be important in terms of understanding itch.

I'm really interested in immune system dysregulation because it's so common in our patients and it just makes sense that this could be important in terms of helping to explain why CKD-associated pruritis takes place when you've got dysregulation at an imbalance in just the hundreds of mediators that are involved in terms of inflammation.

And then I think the area that has really come to the forefront in terms of interest more recently, which is opioid dysregulation and imbalance, substances that we certainly understand well. And when we think about patients that are treated with pain medications or people that misuse opioids, we know that itch is a common complication that goes with that. So could it be that there is some imbalance that takes place in patients with kidney disease that might explain some of what we see?

Dr. Caudle:
That's very helpful and very interesting as well. You know, moving forward with these thoughts, you know, how do these four theories translate into therapies used to manage CKDAP? And what are their benefits and risks?

Dr. Fishbane:
Yeah, thanks, Dr. Caudle. So that's a good question. And I think this is important for us that we consider treatments, but in this context. So if we started, let's just do it the same way. So starting with the deposition of uremic toxins, if we believe that maybe that plays a role in the skin sub-q tissues, well, then we have to look at the efficiency of dialysis and consider that. So, in particular, we need to focus on Kt over V urea reduction ratio and other markers that we use to understand the effectiveness of dialysis. If we're finding that Kt over V is, for example, consistently low, that would be where we'd aim to try to understand perhaps if that's playing a role in terms of the patient's itching.

The second area is peripheral neuropathy. So to the extent that we believe that peripheral neuropathy might be an important part of pruritis. Well, we've got drugs that work in that direction. So we're able to test this because if you have a patient, and I specifically when I have somebody who has pruritis, and they also have neuropathy, and perhaps I'm treating them for other reasons for a typical peripheral neuropathy, I'm more likely to use a drug like gabapentin. And there is data for gabapentin and its use in patients with itching. The concern here might be side effects. So there are a higher rate of side effects versus placebo, things like confusion, dry mouth, visual changes. I think it's a relatively narrow therapeutic window that we've got. But there certainly are some patients where we can achieve a good balance and be able to treat patients for itching. So peripheral neuropathy is important.

And then we get to the subject of immune dysregulation. And when we look at the possibility that one of the causes for pruritis might relate to the immune system, well, that gets us into areas of potential treatments that affect immunity. And this could be as simple as antihistamines. So that using a drug like diphenhydramine to try to decrease the histamine response, it's not very satisfying in terms of treatment. There are previous studies that looked at other agents.

I think the one thing that is kind of time honored here is that UV light therapy is generally fairly effective in terms of uremic pruritis. The problem here tends to be more that for people that are already taking three days a week and devoting it to hemodialysis, it's really hard to devote all of the time required for light therapy. So it hasn't really advanced very far in the time that I've been in nephrology, but now in occasional patients I've used it and have had some success.

And that brings us to the area of opioid dysregulation. So you know, I think this subject right now kind of comes to the forefront because in the U.S. we have a first approved agent for the treatment of uremic pruritis that relates specifically to this subject. So again, look, we know there's opioid receptors in the brain, the central nervous system, but I'm sure you're aware that the opioid receptors are also in peripheral nerves. You'll find them in the skin and keratinocytes, melanocytes, they're in hair follicles. It's really remarkable, but we must note that there is opioid effect in the immune system. And there's kind of overlap here between the previous area that we looked at in terms of immune dysregulation and opioid dysregulation as well. So the concept here with the hypothesis is central new mu opioid receptors being stimulated. Again, we know drugs like morphine, you know, routinely lead to itching. But then there's other opioid receptors. So, antagonism of peripheral Kappa opioid receptors, what effect might be there, and this is something that has been tested pretty significantly in the last couple of years. So we'll speak a little bit more about this particular subject.

Dr. Caudle:
Thank you so much for that, Dr. Fishbane.

Now this brings us to our next polling question. And again, 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 as we move forward, let's go to audience question number two.

So this question reads: How confident are you in your understanding of the clinical trial data regarding new and emerging agents for management of moderate to severe pruritis in your patients with CKD? A: Very confident; B: Moderately confident; C: Mildly confident; and D: Not confident at all.

Let's take a look at what our answers show. We've got 25% that feel moderately confident, that just bumped up to 40%. And minimally competent is about 60%. Now they are about neck and neck. So we will continue to assess this as we move forward.

Let's go back to you, Dr. Fishbane, as we continue to explore these topics. You know, based on the evidence you shared with us earlier, Dr. Fishbane, there doesn't seem to be any approach that is specifically targeted towards opioid dysregulation or imbalance. Can you tell us about the agents currently under investigation, or recently approved that target opioid dysregulation or imbalance?

Dr. Fishbane:
Yeah, great. So let's look at clinical data now. So far, we've become more hypothetically and thinking about treatments that might match with theory.

So I want to start with nalbuphine so this is a mu opioid receptor antagonist and it's a kappa opioid receptor antagonist. There is some data here, 373 hemodialysis patients with moderate or severe uremic pruritis. In this study by Mathur et al, patients were randomized to 60 or 120 of nalbuphine versus placebo for eight weeks, and I think eight weeks is fine. The results were, they found a 3.5-point decline in itching intensity in the group that got the high dose of nalbuphine, but there was no change compared to placebo with the 60 milligram dose. And I think maybe just a little bit disappointing that the change compared to placebo with the high dose of nalbuphine was 0.7. So it's unclear the extent to which that would be noticed by patients and have an effect. So interesting drug. You know, I think we probably need a little bit more research to understand this better and an agent that's not approved in the United States for this specific purpose.

Nalfurafine, so this drug is a peripheral kappa opioid receptor agonist. I like the mechanism. And this is a drug that's approved in Japan, not the United States. But for this drug, there is evidence that both the 5 and 2.5 microgram doses of nalfurafine did reduce itching. And this was in a study looking at dialysis patients compared to placebo. So we'll certainly be interested in seeing whether this extends to studies in the U.S., and whether there's a drug that may eventually be available in the U.S. potentially for treatment of our patients.

Difelikefalin. So that's a long name, difelikefalin. So this drug is really interesting. This now is the first drug that the FDA has approved. And it's approved to treat moderate to severe itching in patients with CKD-associated pruritus who are on dialysis. So for our patients that we talk to that we learn have itching, these are patients that might be candidates. Here's what we've learned. So the drugs have peripheral kappa opioid receptor agonist. It's given three times a week at the end of the dialysis treatment. And it reduces the activity of the sensory nerve. And that's the nerve that's of course relaying the response for itching from the skin to the spinal cord and brain. Adverse events that have been seen with this drug have included diarrhea, some dizziness, vomiting. It's really important to note that the drug is peripherally restricted so it's not getting into the central nervous system. It works on the kappa opioid receptor, not the mu receptor that we've often been concerned about. The mu receptor, of course, is associated with misuse and issues like euphoria and withdrawals. So that's not what this is. This is a drug that works on kappa opioid receptors.

And here's the seminal study. So this was published in the *New England Journal of Medicine* in 2020. And this was called the CALM1 study. So this was 378 dialysis patients. Patients with moderate to severe uremic pruritus. And the patients were randomized to treatment with point five mics per kilogram of I.V. difelikefalin or placebo three times a week for 12 weeks. And what you see here, when you look at the graph on the right, is the percentage of people that had at least a 3-point increase in terms of the Worst Itching Scale, it was 49% with difelikefalin compared to 27% with placebo. And I've studied this subject a lot, so this was kind of particularly exciting for me when I saw that we had such clear positive results and that it extended beyond just itching into improvements in patient quality of life, mood, and sleep. And that's important for us to know that itching, it's not the simple mosquito bite that we get that causes a little itching on our arm, but rather itching that patients on dialysis experience, it just has a much broader effect in terms of the overall quality of their experience.

Now the next study, the CALM2 study, this was published looking at Phase 3 global data, 473 hemodialysis patients. And we're looking here over the course of 12 weeks, a very similar study. And in Panel A, again, we're looking at the 3-point score on the Worst Itching NRS scale that we saw before. And you see again, the very robust effect. The difelikefalin led to a 52% improvement compared to 31% with placebo. Now, I like this because it takes it a bit further now looking at a 4-point improvement. And although in the dermatology world, 3 points is often used as a pretty strong assurance that the patient is having a true meaningful benefit for them, 4 points is a pretty profound effect. And here we see that that was achieved and more than twice the number of difelikefalin patients; 37% compared

to 18% with placebo. Both were highly statistically significant in this large study.

Dr. Caudle:
Dr. Fishbane, that was very helpful. Thank you so much for going through that. So now how do you select appropriate treatment for your patients with CKD-related pruritis?

Dr. Fishbane:
Sure, so you know, I'm not going to be cavalier and say that there is a definite response and answer to this question for all patients. I think individualization is necessary.

So you know, I want to start by going back to Dr. Shirazian's concept. First of all, that there's a lot of itching in this population, and that if we're going to be able to treat it effectively and improve patients' lives, we first have to know about it. So we ask about itching specifically. It's not enough to go through the dialysis unit ask how you feel, patients underreport pruritus. We need to discuss it with patients. And then the history is important. How long have they had it? How extensive? How much of the body is covered? Is there a rash that goes along with it? And what time of day does it affect them? Is it on dialysis?

I like the physical examination because I think if there's a rash that goes along with that, I start to think maybe have some dermatologic conditions. And especially in winter, I know I see a lot of dry skin and that leaves a nice avenue for potential treatment.

Don't forget the biochemistry here. So looking at calcium, phosphorus, parathyroid hormone, the adequacy of dialysis with Kt over V, urea reduction ratios, and BUN and creatinine. But putting together the clinical constellation, then you've got the ability to kind of think about what's going on in patients with uremic pruritus. And if you think that dry skin is an issue, really talk to patients about what kind of soaps are they using, shampoos. And there are some really high-quality moisturizers that I've had some pretty good luck with my patients. For toxin deposition, now I admit I don't see this very often where people have low Kt over V's or low urea reduction ratios. I think in the United States right now, about 98% of patients have Kt over V's greater than 1.2, but it is an area to look at. If a patient has peripheral neuropathy, that's an opportunity to try gabapentin. Be careful. Remember, the window for safety there is little bit narrow, but it is an agent that has some data. It's not approved for the purpose, but I think it's reasonable to try.

When we think that there might be immune system dysregulation, and look, you don't really have a good way of knowing that that's necessarily the case, but there still is a reason to try antihistamines in certain patients, and you'll find some that are already on it.

But opioid dysregulation. Now you don't know if your patient has opioid dysregulation. You don't have a test to be able to do that. But fortunately, in the studies of difelikefalin, it's not like it was broken down into these different causes of uremic pruritis. All we know is that when you take all comers who have uremic pruritus, treat them with difelikefalin compared to placebo, that difelikefalin was clearly effective and pretty well tolerated.

So whatever the cause is there, I think that if you have clear dryness of the skin, moisturizers are an elegant solution. Beyond that, if the patient is not well dialyzed, but I think you're often going to find that difelikefalin is going to be an interesting agent to try for patients, especially if they really have the moderate to severe pruritus that affects their life.

Dr. Caudle:
Thank you for that. And now Dr. Shirazian, let's head back to you for a moment. You know, I would assume that diagnosis and management of CKD-associated pruritis is multidisciplinary. You know, that patients may share their experiences with itching with their nurse or dietitian, for example, possibly more often than with their nephrologist. So how might you develop a multidisciplinary approach to optimize identification and management of these patients?

Dr. Shirazian:
Yeah, thank you. So I think you hit the nail on the head there when you say multidisciplinary. So again, it's not just the nephrologist that is responsible for diagnosing and treating this condition. So I would think of a multidisciplinary approach as involving nurse practitioners, registered nurses, dietitians, social workers, these - this team can educate the patients on chronic kidney disease-associated pruritus. And they can also perform these assessments of itching severity, and they may be able to do so more frequently than the physician. So either monthly or every other month, you can have a quick screening assessment.

Now, if itching is present, at that point, you can see if it's impactful by using a scale that measures both itching severity and the effect on quality of life.

And so if both are present, if a patient has itching and it affects their quality of life, at that point, you can talk to the physician and the physician can become involved. And I think the first step as Dr. Fishbane just eloquently presented is a good history and physical. Make sure you're dealing with chronic kidney disease-associated pruritus here. At that point, you can consider treating dry skin as he said. But if the itching persists, that's when you think about medication.

And once they're on medication, you want to be a little bit more diligent in how you are assessing itching. So I think at that point, you want to use these severity scales either weekly or every other week. And then you can do a scale that assesses severity and impact of quality of life, maybe monthly or every other month, just to make sure you're getting impact with your treatment. And if needed, you might need to up-titrate the treatment.

Dr. Caudle:
Excellent. And as we move back to you, Dr. Fishbane, are there any key take-home messages you'd like to share with our audience?

Dr. Fishbane:
Yeah, so thank you. And I think there's a couple of things here that are really important for us to think about. And really a lot of this just goes back to Dr. Shirazian's presentation that CKD-associated pruritis is far more common than we realize. There's a lot of patients that have this as a problem. And we know that patients greatly underreport it for a variety of different reasons. It's not the same as the mild itch that all of us suffer from, from time to time. This is the kind of itching that really affects somebody's life. And for a lot of patients, it really gets into quality of life and life experience sleep quality. And it becomes, because of that, increasingly important that we address it, that we ask patients very specifically.

There's different factors as we saw that can contribute to the pruritus, and that can help us to some extent, in terms of how we choose to treat. There are numerous agents like diphenhydramine and difelikefalin that are out there. It's good to be able to, I think, direct therapy and try to use non-pharmacologic agents, if you can, perhaps diphenhydramine initially and then moving up towards difelikefalin if you have patients with more significant problems.

But it is, you know, I think, a particularly exciting time. I've been interested in the subject for 15 years and had a lot of frustrations. So really good to see that in August of 2021, that the FDA did approve difelikefalin for use in this population.

But as you see on the bottom, really the most important part here that we can't help patients unless we're talking to them about their problems with pruritus. So we need to ask patients, we need to ask them, do they have pruritus as a problem, and the frequency and the severity? Thank you.

Dr. Caudle:
Well, thank you very much, Dr. Fishbane. Your dedication and also Dr. Shirazian, your dedication as well is immediately evident to us all. I want to thank you, Dr. Fishbane, for your take-home messages.

We're now going to transition to our Q and A portion of the activity. If you would like to participate, we hope that you do, please submit your questions by typing them into the chat control panel on your left or via Facebook Live. Now it looks like we've got some questions that have already come through. So we're going to begin with some audience questions. And the first goes to Dr. Shirazian.

Dr. Shirazian, you know, how do we know when a patient's pruritis warrants actual investigation and possible medication?

Dr. Shirazian:
Yeah, so that's a really good question. I mean, as Dr. Fishbane said earlier, we all have experienced itching, and it might just be a very minor mosquito bite or something, you know, like dry skin. But when does it rise to the level of needing medication? I think that for patients on dialysis, if it's affecting their quality of life, at that point, it rises to require more investigation and possibly treatment. So is it affecting their sleep? is it affecting their mood? You know, when that happens, it often affects their adherence with dialysis and then it can become deadly. So if they're itching so much that they're not sleeping, they feel horrible, they become depressed, and they don't come to dialysis, you know, then it really has to be investigated and treated. And that does happen. So it's really how it's affecting their life.

Dr. Caudle:
You know, I think that's a really excellent point. Very excellent there, it makes a lot of sense.

You know, sticking with you Dr. Shirazian, we have another question that's come in. This participant asks: If we have optimized dialysis effectiveness, how do we then select the most appropriate treatment?

Dr. Shirazian:
Yeah, and this also goes back to Dr. Fishbane's point. I mean, he, as he said, 98% of patients, at least in the United States are meeting dialysis efficiency guidelines with the Kt over V of over 1.2. And we're constantly, as nephrologists, trying to optimize CKD-MBD parameters. And we look at that constantly, probably twice a month. So that's generally already being done.

I think at that point, you know, we can look for dry skin. If dry skin is there, then we can try to treat that. But as I said earlier, that often just kind of improves the problem but doesn't completely take away the problem.

And then you know, taking a pathophysiologic-specific approach, you know, it sounds nice, and there are probably 34:45___ pathophysiologies; however, there's not that much to inform which one is going on. I mean, if someone - if there's someone with a clear neuropathy, maybe you want to try a medication that targets neuropathy. Inflammation, a lot of dialysis patients are inflamed. If you think yours is particularly inflamed, then maybe you try something in the anti-inflammatory realm. But I think, you know, in general, you would go for the one that it has been approved if there's no clear - FDA approved if there's no clear theory or pathophysiology that you can point to.

Dr. Caudle:
Sure, sure. Thank you for that. And it looks like our next question is for Dr. Fishbane. This participant asks: Is there a way to determine which of those theories and thus which treatment approaches may be most relevant for a specific patient?

Dr. Fishbane:
Yeah, thank you for the question. So I guess, Dr. Shirazian just answered that question, but let me amplify then that, so we could put down on a slide and, you know, clearly show that there are these different possibilities in terms of hypotheses for what might be causing it. Now, you know, as Dr. Shirazian said, if you look at a patient and their skin on the legs is clearly dry, everybody knows, you know, in winter, what this looks like when you're seeing a patient - although I actually saw a patient today, with exactly this issue - that's a great opportunity for the use of moisturizers.

Unfortunately, what we put up on a slide in terms of hypotheses is a little bit difficult to separate in the clinic so that, well, yeah, if somebody has inadequate dialysis, you can address that issue. If there is a clear peripheral neuropathy, then there is a pretty good chance that the itching might be related to that, especially if it's in the same part of the body. So if I have a patient where at nighttime, they're noticing they're having pain in the feet, and during the day they're having itching in the legs, I do like to try in those kind of patients, something like gabapentin. But generally, look, I mean, it's really hard to separate. We don't have tests that will yet be able to separate patients into these different theories of cause for pruritus.

So, you know, I think we will always do well to start a little bit conservatively. And if we're not doing well with a patient and bringing them fulfillment in terms of the symptoms, then I think the fact that we now have an approved treatment, and difelikefalin gives us a lot more therapeutic flexibility in terms of our ability to really address the issue.

Dr. Caudle:
Excellent. And Dr. Fishbane, let's stay with you for a moment with difelikefalin. For how long would patients stay on that drug? What are your thoughts about that?

Dr. Fishbane:
Yeah, thank you. Really good question for whoever asked that one. So we don't definitively know the answer to that question yet. And the Phase 3 studies were not really designed for the purpose. So I've kind of, in my own mind, worked out, you know, the way that I will be addressing this, and that is that when I have a patient where itching has been a really significant problem that's affected their lives, I'm going to be putting the patient on treatment for at least three months, and just making sure that I really smother out the problem completely. And at that point, I might try a trial with a patient off, see how they do, and then reconsider and reevaluate, you know, as I continue to see the patient and see whether symptoms re-evolve.

Symptoms tend to bounce back when you stop difelikefalin . So we have to kind of keep that in mind. And pruritis can be a little bit of a transient problem in some patients. So we also don't want to commit the patient to 15 years of therapy.

So you know, certainly a need to kind of continue evaluation over time for individual patients.

Dr. Caudle:
Excellent. Thank you so much. We only have a couple minutes left. We got one more question that I would love a quick answer from you Dr. Shirazian, because I think it's an excellent question. This participant asks: Do you ever - do you find you ever need to work with a dermatologist for additional treatment of pruritus? Very quickly, what would you say to that?

Dr. Shirazian:
Well, I would say quickly, it's very difficult to get our patients in with specialists and particularly dermatology. So my - I would ask the question back: Have you ever tried to get your patient in with a dermatologist? And often it's very hard to get timely consultations for specialists in dialysis patients. But besides that, dialysis patients, they really don't like to spend much extra time seeing doctors outside the dialysis unit, because they commit so much of their time at the dialysis unit. So whenever you can, it's good to act as the primary care doctor.

Now that being said, I've involved them once or twice for UVB light therapy. Other than that, I haven't, and I personally think this is an

issue that the nephrologist should be able to handle.

Dr. Caudle:
That's excellent insight. Thank you, so - oh, I'm sorry. Go ahead Dr. Fishbane.

Dr. Fishbane:
Look, if I see a skin issue that I don't feel that I recognize well, you know, I really want the dermatologist to be part of treatment. But you know, one, it is really hard to get access to dermatology consultation. There's often a three or four month-wait to get the patient in. And two, most of uremic pruritis, we can probably manage. I think that that's within our realm as nephrologists.

Dr. Caudle:
Excellent. Excellent. You know, not to cut you gentlemen off. This was really a wonderful discussion. This is a great way to round our discussion on chronic kidney disease-associated pruritis. I'd love to thank my guests, Dr. Shayan Shirazian and Dr. Steven Fishbane, for helping us better understand the epidemiology of CKDAP, its pathophysiology, and pathways associated with current treatments, and the clinical trial data on new and emerging treatments. Doctors Fishbane and Shirazian, it was so wonderful having you on the program. It was great speaking with you today.

Dr. Fishbane:
Thank you so much. It's really been great to be part of this.

Dr. Shirazian:
Thanks for having me. Thank you.

Announcer:
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