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KALMing the Itch: Improving QoL in Patients with CKD-aP

Announcer:
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Dr. Topf:
Chronic kidney disease-associated pruritus, or CKD-aP. We used to call this uremic pruritus. The new name is going to be CKD-aP. This is a distressing symptom for patients with chronic kidney disease, primarily hemodialysis patients, but not exclusively. And this is an area where we're developing a lot of new information, both epidemiologic and therapeutic. This is a condition that really detrimentally affects our patients' quality of life. It affects their sleep, it's associated with poor outcomes, and it's something that we're learning about, and we're finding new treatment paradigms. And so what we're going to be talking about today is how do we implement screening programs to find the patients that need these therapies, and how do we apply recent clinical trial data to improve the quality of life and the existence of our patients?

This is CME on ReachMD. And I am Joel Topf.

Dr. McCafferty:
And I'm Dr. Kieran McCafferty.

Dr. Topf:
We have a lot to talk about today, so let's begin. Kieran, I know you have a case for us. Let me have it.

Dr. McCafferty:
So it's Mr. Ali, who's a 65-year-old man with end-stage renal failure due to diabetes, as is all too commonly seen in our patients in East London. He's been on in-center hemodialysis since 2020 for 4 hours, 3 times a week, fairly uncomplicated dialysis. Although he's been experiencing increasing itch over the last year and has been taking antihistamines for the last few months with little effect. So he came to see me and was complaining of itch.

And I think some of the points that we want to raise are really the misunderstanding about itch, and often, you know, historically when we were asked of patients who were itching, we would say, "Ah, it's because you're not getting enough dialysis," or "Oh, it's because you're not taking your phosphate binders religiously enough, and phosphate's high." I think, you know, from what we know from epidemiological data, that is not the case, and we need to get away from that idea.

Dr. Topf:
And it actually brings something up. Kieran, did you ask about the itch, or did the patient bring that up to you?

Dr. McCafferty:
So I must say, as a bit of an itch convert, I often ask my patients do they itch. But I may be greater than 2 standard deviations from the mean of people who are interested in itch, I guess, but that will change hopefully with this podcast.

Dr. Topf:
Yeah. And that's what we see when they do surveys of medical directors and nephrologists: doctors tend to underestimate the burden of itch on patients.

Dr. McCafferty:
We know that it's common, so we you know that 40% of our dialysis patients across different countries experience itch.

Dr. Topf:
And I think another thing that happens is these patients come to the dialysis unit, they complain of itch, they get the diphenhydramine, and it puts them to sleep. And it's also probably a good idea to talk to the techs and talk to the nurses and find out patients, is anybody taking a lot of diphenhydramine? Are you finding people that are trying to suppress their symptoms during dialysis, and maybe offer them a better option. Because [if] that diphenhydramine doesn't help them, when they leave the dialysis unit, that itch can continue then.

Hey, Kieran, do we have a sense of how prevalent itch is among dialysis patients?

Dr. McCafferty:
We often underestimate the prevalence of itch, because really, we don't tend to ask our patients rigorously, routinely, are they itching and how much are they itching. You know, we are busy clinicians; we've got a lot of other things that we need to get through in terms of in patients. But I think it's about raising up the priority.

I think in terms of how do we assess someone is itching, there are a lot of tools that we can use to perhaps more quantitatively assess itching, certainly the WI-NRS or the Worst [Itch] Intensity Numerical Rating Scale, or "winners." It's a really good way; in other words, it's quick. It's in the last 24 hours, can you tell us how much you're itching on a scale of 0 to 10? So it's pretty easy for everyone to understand. And that's a really good way of establishing maybe, you know, coming back a week later to track trends.

Dr. Topf:
Yeah, well, Kieran, you've been dancing around the idea that there's this new therapy. And that therapy is difelikefalin. And we're using that in our units. When I'm screening my patients, I just merely ask, like, "Are you itching?" And, you know, when you open the door, patients are pretty forthcoming with that. And then if I need to use a difelikefalin, they end up getting the WI-NRS scale to determine whether they're eligible for that.

Dr. McCafferty:
Yeah, and I guess up until recently, we were pretty limited in what are the therapies that we could use for our patients. And certainly, I routinely recommend patients using moisturizing cream, because [it's] safe, it's cheap, and you know having dry skin will potentiate the effects of itch.

The other therapies that we can look at, like you said, sort of antihistamines and gabapentinoids. You know, we use them quite a lot. And we use them in the UK, you know, there's not a huge amount of evidence. There's quite a bit of evidence that, you know, certainly in the gabapentinoids, there are significant side effects. And even with the antihistamines, like we said, you know, they cause significant sedation, and sometimes patients might use them if they itch, particularly at night, almost as a sedative just to get them through the night so they sleep better, rather than a treatment for itch.

Dr. Topf:
Another therapy that's out there and is always listed is UVB therapy. I've had patients get that, but it's pretty difficult to get. It's a time-intensive therapy that requires them to find a dermatologist that can offer that.

For those of you just tuning in, you've been listening to CME on ReachMD. I'm Dr. Joel Topf, and I'm here with Dr. Kieran McCafferty. We're discussing the treatment paradigm of CKD-associated pruritus and new therapies available for its treatment.

Do you have a schema in mind when you approach a patient who complains of itching?

Dr. McCafferty:
NICE, so the UK National Institute of Clinical Excellence, kind of are the gatekeepers for new therapies for the UK. They approved the recommendation for difelikefalin for people with CKD-associated pruritus. So we're now all working full steam ahead to try and get this up and running in all our dialysis units. And the great thing about NICE in the UK is once you've got NICE approval, you're golden; you have to be able to provide it. And so, like you're doing for people who we will be starting on difelikefalin, we want to see at least moderate to severe pruritus based on a WI-NRS. And ultimately, were both evidence-based medicine doctors, and then also we'd be checking maybe the WI-NRS at 12 weeks, like in the study, to ensure that patients are getting benefit from this medicine. And if they are, we can continue it on.

But I guess we spoke a lot about the trial data. So did you want to talk us through why we're so interested and why we're so lucky to be having this new therapy from the trial point of view?

Dr. Topf:
Yeah, so there are 2 trials that were done. There was KALM-1 that was done in the United States. And then there was KALM-2, largely the same study criteria. They enrolled patients with CKD-associated pruritus. They got them on a WI-NRS scale, they had elevated, significant itching, and they were randomized to drug or placebo. They received the drug for 12 weeks. And then there was an extension after that to continue them through 52 weeks.

This drug is a kappa-opioid receptor agonist. And there is basic science research to show that CKD-associated pruritus is due to imbalance of opioid receptors and their activation. This is a way to restore some of that balance. There are some other kappa-opioid receptors that have been tested; they have had effect. One of the problems with kappa-opioid is that if it enters the central nervous system [CNS], it causes pretty significant depression. And so one of the things that makes difelikefalin unique is it is locked into the peripheral circulation. It's unable to enter across the blood-brain barrier; it doesn't have that CNS penetration. And that's actually super useful. So not only does not cause the dysthymia that you get with the kappa-opioid receptors, but you don't get the opioid addiction that you can get with any kind of opioids. One of the components of these trials was a washout at 2 weeks. And during that washout period, patients were screened for any indications of opioid dependence. We didn't see any, so that was a big deal.

And so what you had is about a 30% response rate in the placebo group and about a 50% response rate with the difelikefalin. So significant improvement, and one of the things that I have found with my patients is oftentimes they'll take the drug for 12 weeks, and they're kind of, their itch goes away, and they no longer need therapy after that. So I think, you know, giving a drug holiday after 12 weeks is a reasonable thing to experiment with and to see if your patients is still needing it or benefiting from it. But in my experience, these patients get rather brisk response usually within a dose or 2. What have you seen?

Dr. McCafferty:
I think it's what's really important and what a really reassuring aspect of the data is in the open-label period, when the patients who didn't know whether they were on placebo or not went open label and got the drug therapy, there was an additional benefit so that they became even less itchy, even if they were on the placebo and had a placebo effect. So this is definitely a real effect beyond just being desperate for a therapy area.

Dr. Topf:
Yeah, absolutely. And, you know, you're pulling a rabbit out of the hat once, KALM-1 is good, but do it a second time in KALM-2 and still get significance is really important also. Yeah, it is compelling stuff. This definitely does work.

What about side effects? So the drug [is] pretty well tolerated. The biggest aspects were GI [gastrointestinal] side effects, diarrhea, nausea, vomiting, and dizziness. In my hands, I haven't seen those side effects. What about yourself?

Dr. McCafferty:
No, I was surprised that, you know, running the clinical trial, we were obviously very, very closely monitoring them, and I was surprised how well tolerated they were. Obviously, we didn't know whether they were on placebo or the IMP [investigational medicinal product]. But, you know, dizziness, diarrhea, vomiting is really common in our dialysis patients. They're very comorbid. And in doing any trials in hemodialysis, you've got so many AEs [adverse events] just because these are very frail, comorbid patients. But you know, there was a signal for you know, GI, like you say. But really, you know, still low numbers, sort of 10%, 12%, or maybe, you know, between 7% and 10%, something like that.

Dr. Topf:
Are you taking any specific precautions in your patients that you're giving difelikefalin?

Dr. McCafferty:
So I'm a kind of a purist when it comes to trial data that anyone that I would enroll into the KALM-1 or KALM-2 studies, I would offer therapy for difelikefalin, being mindful that one of the exclusion criteria for the KALM-1 and KALM-2 studies is a history of opiate use.

Dr. Topf:
Anybody that's complaining of itch, I'm offering this to them if we're unable to get a response with creams. One of the things I do do, is we want to make sure that after dialysis they're not dizzy, their blood pressure is stable. There was not a fall signal, which is great to see. But I want to make sure before these people get in the car and think that they're fine, and they're not dizzy and we're not kind of concerned there. But largely, well tolerated drug, I'm impressed.

Dr. McCafferty:

If I was going to start it, we would, again, use it like what we've done for the trial. So we'd give it at 0.5 mcg/kg, at the end of dialysis. We know that it's renally cleared, and it's cleared by dialysis. So in some ways, dialysis patients are the ideal patients to receive it. They get it at the end of dialysis, and it lasts in their system, is dialyzed out on the next dialysis session, and then they get it at the end of their next dialysis session. So you know, patients don't have to remember to take it. There's no problems with adherence, and it lasts steady state in between dialysis sessions. It's really an ideal drug for patients to use.

And so how long should we wait after starting difelikefalin before working out whether it works or not?

Dr. Topf:
So you remember that only about 50% of patients respond to difelikefalin. Half of them will respond in the first month, and 88% respond by 12 weeks. And so, you know, don't give up on the drug if they haven't responded by the first month because half the patients will respond after that. Right? It's just too early. But by 12 weeks, if the patient hasn't responded, it's unlikely that they're going to respond. A few people do respond after that, but not many. And so I think 12 weeks is a great breakpoint in terms of taking a look at this medication.

Dr. McCafferty:
It also aligns with the primary endpoint of the KALM-1 and KALM-2 studies, I guess.

Dr. Topf:
Yep, and you can feel like you're in KALM-1 or KALM-2. You can pretend you too were a PI.

Well, this has certainly been a fascinating conversation. But before we wrap up, let's each provide a take-home message for the audience. Kieran, what have you got?

Dr. McCafferty:
So I think the thing that I would say is the most easiest thing is ask your patients do they have itching. Because I think, well, if we don't ask them, often, they won't tell us. And if we don't know that they're itching, we can't offer them the therapies that will make them better.

Dr. Topf:
Yeah, and then the other thing that I would say is I would emphasize that, hey, there are new therapies available; we've learned more about this condition. So if your patients have asked about this in the past, kind of go in with an open mind, say, "Hey, there's some new options here, and they are both effective and safe." And so this is something that bears exploration.

Dr. Topf
Unfortunately, that's all the time we have today. But I want to thank our audience for tuning in. And I want to thank Dr. Kieran McCafferty for bringing an interesting case and joining me for this great discussion. This was really a lot of fun. And I think—I hope everybody learned something today.

Dr. McCafferty:
Thanks again. I hope everyone found it useful. I hope people find it valuable, and I hope people ask about itch.

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