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Getting to the Root of CKD-Associated Pruritus: Questions From the Field

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Dr. Topf:
Patients undergoing dialysis for chronic kidney disease often struggle with CKD-associated pruritus, or CKD-aP. This symptom is linked to diminished quality of life, compromised sleep quality, and heightened levels of depression. But it's also associated with adverse clinical outcomes such as susceptibility to infections, higher rates of hospitalizations, and elevated mortality.

Now let's address some frequent inquiries from the field concerning the management of patients with CKD-aP.

This is CME on ReachMD, and I'm Dr. Joel Topf.

Dr. Burton:
I'm Dr. James Burton.

Dr. Topf:
James, we know that CKD-aP significantly impacts the quality of life of patients on maintenance hemodialysis, yet it remains considerably underreported. How can we get better at identifying these patients to enhance their quality of life?

Dr. Burton:
Thanks, Joel. That's completely true, actually, about the impact on quality of life. And how can we really address that without knowing who the individual people are? And if we know from DOPPS [Dialysis Outcomes and Practice Patterns Study] data that somewhere between two-thirds and three-quarters of people on maintenance hemodialysis report any pruritus at all, and a considerable number of those, more than 40%, would report moderate to severe pruritus. They don't actually tell us as healthcare professionals about those symptoms. So it's very difficult to actually identify those people.

So how can we get better in identifying them to enhance their quality of life? The first thing is to go out and ask people about whether they feel that itch, given that we know that they are there, on dialysis, experiencing those symptoms and probably being quite silent about that. Once we've been out and we've proactively identified them, then we can think about doing something to improve their quality of life.

And there are some different tools that we can use. We can think about proactive assessment with patient-reported outcome measures. One of the ones would be the Worst Itch Numerical Rating Score [WI-NRS], which were used in the clinical trials.

And I guess, Joel, what would be the clinical features that you look for to differentiate between CKD-associated pruritus and other types of pruritus in our patients to make sure we're really picking up the right people to start treating?

Dr. Topf:

Well, James, I completely agree that the thing that we need to do as clinicians is start asking about itch. And patients, for so long, have not had good treatment opportunities available to them. And I think they've just started to swallow this complaint and not mention it to us because there was nothing that we could do. And so I think we need to take the proactive step of just asking them if they have itch.

Then the locations of the itch, you know, typically it'll be a trunk, back, face, and arms are kind of classic locations. But I think the overriding view that I have when I think about this is that the pretest probability that it's CKD-aP is incredibly high. If you have a dialysis patient complaining of itch, it's likely CKD-aP. It's worthwhile doing an exam to see if there's any other primary skin abnormality that's causing it, but likely what you're dealing with is CKD-aP.

Dr. Burton:
I just want to reiterate what you said, which is to ask people, “Do you itch?” That's the first thing, irrespective of the scores and things out there.

The other thing would be we just need to make sure we don't delay looking for other causes of itch, because most of the time it is going to be CKD-aP, and delaying might cause a prolonged period of time where people have got this symptom.

So, Joel, antihistamines, off-label gabapentin, we often use those to manage our patients with CKD-aP, and they have limited benefits, if any. Do you want to talk a little bit about that?

Dr. Topf:
We're coming from a world where we had very few effective or no effective treatments for this. And so we would use what we had available. And so antihistamines do have an anti-itch property for lots of skin ailments, right? If it is going to be histamine-generated, you will find a benefit from antihistamines. Though patients with histamine-generated itch tend to have a kind of a wheal and flare formation, right? We're familiar with those allergic reactions and what they look like on the skin. We don't see this in CKD-aP. And not surprisingly, antihistamines do not work for this.

Now, antihistamines are sedating, and oftentimes, a patient that’s complaining of itch, if you can put them to sleep on dialysis, they’ll stop complaining about itch. But don’t misinterpret the fact that the patient fell asleep as a win here. Right? The fact that these drugs are sedating does not mean that they’re anti-itch, and in all the clinical trials that I’ve seen, antihistamines are not effective for CKD-associated pruritus.

The other drugs that we reach for are gabapentinoids. And these have been studied in CKD-aP and they do have some efficacy. But the downside is something that we’re all familiar with. These drugs have a lot of neuroactive side effects, and we see consequences of gabapentinoids in our patients all the time. And we’re all aware of the strict dose limitations in dialysis patients because we keep running into neurologic side effects from these drugs.

Dr. Burton:
You’ve highlighted the real main point there, which is every time we do anything as an intervention, it’s all about the risk of the intervention versus the reward. The risk of those and the burden of those far outweigh any benefits that they get in terms of the relief of their CKD-aP.

Dr. Topf:
For those just tuning in, you’re listening to CME on ReachMD. I’m Dr. Joel Topf, and here with me today is Dr. James Burton. We’re discussing common inquiries from the field concerning the management of patients with CKD-aP.

Dr. Burton:
I’m interested to hear, Joel, your therapeutic approach for patients with CKD-aP. What do you do?

Dr. Topf:
So I usually start out with moisturizers. If you use moisturizers and can heal the skin or improve the health of the skin, just do those. And there’s actually pretty good data on using skin moisturizers to improve CKD-aP.

And then if that doesn’t work, you know, in the past, I would go and use low-dose gabapentinoids. But I’ve just skipped that now; I’m going right to difelikefalin as an IV medication at the end of their dialysis treatment because, A, I know that it works, and, B, it has actually pretty good side effect profile. And so that’s kind of my 1-2 step.

What are you using?

Dr. Burton:
So I’m straight in there with you on that, actually, because we have been using a lot of gabapentinoids, accepting that it doesn’t work for many because of the side effects. But now we’ve been using difelikefalin and seeing just how good it is as a treatment for the relief of

CKD-aP. We've used that approach, which is pretty much straight in with difelikefalin, with really good impact, actually, after the use of moisturizers.

Dr. Topf:
Excellent.

Dr. Burton:
Joel, so I think we're in agreement then that we would both be reaching for the difelikefalin fairly early in the treatment pathway.

You've been involved in the studies. Any reports about safety or other concerns for our patients on dialysis or with other comorbidities?

Dr. Topf:
There was some dizziness and there was some concern for falls with the use of difelikefalin. This is not something that I've been running into. I mean, my patients, at the end of dialysis, they oftentimes are unsteady. It was difficult to see a difference between the difelikefalin patients and placebo patients in that, though we did detect some of that in the studies. And so that's one of my concerns. But honestly, using the drug, it has not been problematic, and it hasn't been something that has limited us from using the drugs when we've done that.

How about yourself?

Dr. Burton:
We've found the same. You know, the patients that I've started in it, it's been well tolerated and it's certainly very effective.

The other thing that people might ask would be about the duration of treatment then, Joel. Would you worry about treatment in the long term?

Dr. Topf:
So in the KALM-1, and KALM-2 trials that we did, we did not find that these drugs wore out, that these continued to be effective therapies for as long as patients took them. What I'm finding clinically is that these episodes of pruritus seem to come and go in waves and that you can treat that and knock that down, and then patients can go off the medications when they're no longer having tremendous itch. And so that has been an approach that we have taken, and that's been effective for us, that patients will have episodes of just intolerable itching, you treat it, it seems to go away, and they're okay for a while.

What about yourself?

Dr. Burton:
I think that's right. And the other thing that we've seen is looking a little bit about symptom clusters and thinking about the other symptoms that sit in that skin cluster. So problems with sleep, for example, problems with mood. And I think what we've demonstrated through the trials is that those individuals who get more than a 3-point resolution in their WI-NRS scores, you can see really considerable improvements in their sleep and also in their mood.

Dr. Topf:
Difelikefalin is a kappa-opioid agonist. Because of its structure, it's really limited to the systemic circulation and doesn't penetrate the blood-brain barrier. And this was a concern for us because there's been some other kappa agonists that have really caused dysphoria. And the fact that you're finding just the opposite, these people's mood improves and that their sleep improves, is really a pretty significant win for this drug.

The other concerns that some people have is that since it's an opioid agonist, is there an addiction potential? And I know that this was a very specific part of our protocol, that we had patients on these drugs for weeks, months even, and that we would then stop them, and we did specific surveys and assessments to see if they had any signs of opioid dependence, and we didn't find any, kind of further backing up that this drug just doesn't get into the central nervous system.

One of the important things that may have been lost when people look at the primary outcomes of KALM-1 and KALM-2, is there was an open-label extension, and these patients continued on difelikefalin up to 52 weeks, and they got a continued suppression of their itch and continued maintenance of their itch. And so the drug doesn't just work to suppress it; it keeps it away.

So one question that comes up is when do you abandon this drug and find that it doesn't work? The majority of patients did get an improvement, but not everybody. And what we found is that most people, if they're going to get a clinical benefit, will get a clinical benefit by 12 weeks. There's a few people that will fall later at 4 months, but after about 4 months, we're not seeing much more additional efficacy.

Dr. Burton:
We've seen exactly the same. And in our follow-up here in the UK, we expect to see patients every 8 weeks or so in outpatients. And I think what we would do is we would obviously be asking about improvements during that time. And if we haven't seen a sustained and significant improvement by the second time we see someone, so at 4 months, we'd discontinue the drug.

Dr. Topf:
Well, this has certainly been a very informative conversation. Before we wrap up, James, what's your one take-home message for our audience?

Dr. Burton:
I think that's probably really easy for me, Joel, and I'm probably going to steal your one which is go out and ask your patients, "Do you itch?"

Dr. Topf:
Yeah, you stole mine. I think that's the biggest thing is that we have good data that patients aren't telling their doctors that they itch. They're concerned about their itching, they're reporting it as a problem, but they're not mentioning it to their doctors. And when you ask doctors, doctors consistently underestimate the burden of itch in their patients.

That's all the time we have today. So I want to thank our audience for listening in and thank you, Dr. James Burton, for joining me and for sharing all of your valuable insights. It was great speaking with you.

Dr. Burton:
You too, Joel. Thanks very much.

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