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https://reachmd.com/programs/cme/stuck-on-antihistamines-for-managing-patients-with-ckd-ap-time-to-reconsider/37607/

Released: 03/31/2026
Valid until: 03/31/2027
Time needed to complete: 15 minutes

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Stuck on Antihistamines for Managing Patients With CKD-aP? Time to Reconsider!

Announcer:
Welcome to CE on ReachMD. This activity, titled “Stuck on Antihistamines for Managing Patients With CKD-aP? Time to Reconsider!” is provided by Medtelligence.

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Dr. Lanot:
Hello. Despite the availability of effective and guideline-recommended therapies, medical clinicians still reach for antihistamines as their first-line option for managing CKD-associated pruritus. So join us today as we are going to walk through a real-world patient case from a multidisciplinary perspective and consider best practices for the diagnosis, the treatment, and the management of CKD-aP.

This is CE on ReachMD, and I am Dr. Antoine Lanot. Thank you for joining us.

Dr. Yosipovitch:
And I'm Dr. Gil Yosipovitch.

Dr. Lanot:
So let's get started by taking a look at a recent patient from my dialysis unit. I think it's a case that is really capturing the challenges we often face. He's a 62-year-old man with polycystic kidney disease who has been on hemodialysis for about 1 year. And in our unit, we have set up a systematic screening program for pruritus, which is led by our nurses every 3 months. That's how I learned that he had been dealing with severe itch. And what really struck me is that he had never mentioned it to anyone—not a nurse, not a doctor—even though he had been suffering from itch for at least 3 months.

So of course, we started a proper diagnosis workup, and we noticed that the only visible skin lesions were clearly secondary to scratching. So we planned exams to rule out the other causes of chronic pruritus, such as allergy, infection, liver condition, just to name a few. And we made the diagnosis of CKD-aP, and it was a severe one, because his WI-NRS score was 7 out of 10, and the itch was really affecting his quality of life.

He described the cluster of symptoms that had appeared recently with sleep disturbances, anxiety, reduced sexual desire and function, and the itch felt uncontrollable, almost life-defining. And it came with this profound sense of shame and social isolation.

I feel that this is something we see far too often. The burden of the disease is real, but it's also largely invisible unless we actively look for it. And first, he had been prescribed antihistamines, but they had absolutely no effect on his symptoms.

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So, Gil, as a dermatologist, is this patient consistent with the patients you see in your practice?

Dr. Yosipovitch:
Yes, Antoine, we see a lot of these patients. And I have to mention a lot of times these patients, in the US at least, they're in dialysis units. They're seen mainly by nurses, and doctors don't ask about their itch, so they come with a diagnosis maybe that they have eczema or some allergies, and basically they have itch related to chronic kidney disease on their dialysis.

So it's important first to differentiate and then have a good diagnosis.

There is a large list of conditions that can cause itch, and clearly one of the questions you have to ask is whether it's a primary rash, because they can have secondary skin changes that look like a rash. They have sometimes excoriations, prurigo lesions that are nodules from scratching. They can have also, very commonly, dry skin. And therefore, it's important to note that these are secondary changes that could be associated with their itching and this is not a different disease.

So putting a good differential is crucial here, but understanding that chronic kidney disease, end-stage renal failure causes itch is extremely important.

It's also important to understand that these patients have been on—it's unfortunate, but still, a lot of these patients are receiving antihistamines, but their yield is so minimal. They have some sedating effect, but beyond that, they really don't target the pathway of itch of this condition.

And in addition, it's important always to note that the majority of these patients have generalized itch, so it's not a localized itch to one site. And that's another important clue in treating these patients, because if it was just a localized itch, maybe topicals could help.

So I think that we share in common a lot of these patients, and unfortunately, there is an unmet need to treat them.

Dr. Lanot:
So when we talk about managing CKD-aP, some universal measures remain unchanged. First, the clear need for daily use of moisturizers, as you mentioned, and also providing adequate dialysis, of course, with a single-pool Kt/V target of 1.4 for the patients in hemodialysis.

Over the past decade, we have made real progress, and the pathogenesis of CKD-aP is now much better understood. We know today that the itch signal in CKD-aP is carried through non-histaminergic nervous pathway. We also now understand that several interleukins, especially IL-31, are involved, and importantly, there is an imbalance between the mu and the kappa-opioid receptors in CKD-aP.

The shift in understanding has really paved the way for more targeted therapies, and this brings us to the new European S2k guideline on chronic pruritus, published in August 2025 in *Acta Dermato-Venereologica*. Several parts of this guideline focus on CKD-aP, and it gives a clear recommendation for the use of the kappa-opioid agonist difelikefalin in CKD-aP.

So now, in other words, DFK is positioned as the standard of care. It is supported by strong clinical evidence with consistent improvements, not only in itch severity but also in sleep and overall quality of life.

There are other options which are much more limited. As you said, antihistamines, they have been long used as the first-line treatments in nephrology, but we understand now that they should not be effective because histamine simply isn't the main pathway.

And we also have the gabapentinoids, which have shown some efficacy for treating CKD-aP in a few RCTs, but they have a very narrow therapeutic index, and in dialysis patients, their use comes with safety concerns because it was associated with risks of altered mental status, dizziness, falls, and even fractures.

So the last point, of course, is that DFK is currently the only drug approved by both the FDA and EMA specifically for the treatment of moderate to severe CKD-aP in hemodialysis.

For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Antoine Lanot, and here with me today is Dr. Gil Yosipovitch. We're

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taking a look at CKD-aP—why and how we should be moving past antihistamines to help our patients improve their quality of life.

Dr. Yosipovitch:
I would mention that, in my practice, for a long time, we have not used any antihistamines, and I don't use them—even the nonsedating ones don't really have any role.

Dr. Lanot:
And probably we could talk about the mechanism of action of difelikefalin because this is quite different from the other treatments that we had previously.

And we remember that in CKD-aP, there is an imbalance between the mu and the kappa-opioid receptors in favor of the mu ones, which are pro-pruritogenic. So DFK is a selective kappa-opioid receptor agonist. That means that it targets kappa-opioid receptors, which are located on sensory neurons and also on immune cells, and it tends to re-establish the physiological equilibrium between kappa and mu receptors.

And something important is that it acts peripherally, without crossing the blood-brain barrier like traditional opioid. This peripheral action is what provides itch relief without the central side effects we often worry about.

So the mechanism is strongly supported by the two phase 3 trials, KALM-1 and KALM-2. And the results of these 2 RCTs were consistent, and they included 851 participants with moderate to severe CKD-associated pruritus. In the pooled analysis of these 2 trials, 51% of patients treated with DFK achieved at least a 3-point reduction on the WI-NRS score, compared with 35% in the placebo group. And the benefits extended beyond itch intensity, with significant improvement in the 5-D Itch and in the Skindex-10 quality of life scales. The effect was quite rapid, with significant separation between the 2 groups as early as week 1.

And recently, we had some additional studies which were published this summer which was quite interesting, in which the authors analyzed the correlations between the circulating level of 20 inflammatory markers and the intensity of pruritus at baseline and after 12 weeks. They found a strong correlation between the itch intensity and the levels of several circulating inflammatory markers, especially the IL-31, CCL2, CXCL10, TSLP, and nerve growth factor.

And what was more striking are the results of the analysis after 12 weeks of treatment, because in patients who responded to DFK, the level of biomarkers decreased significantly, whereas the levels did not decrease in nonresponders, nor in placebo-treated patients—even among those who reported symptomatic improvement.

So this provides the evidence that, in addition to its action on peripheral nervous system, DFK also has an anti-inflammatory effect. And kappa-opioid receptors are also present on immune cells and keratinocytes. Their activation may downregulate inflammatory mediators such as IL-31 and TSLP.

So we can retain a dual mechanism of action: first, neuromodulation with an activation of peripheral kappa-opioid receptors on sensory neurons, reducing the transmission of the itch signal; and two, immunomodulation through an activation of kappa receptors located on immune cells, reducing inflammatory cytokines production.

And this is the first time a treatment for CKD-aP shows both a subjective improvement in patient-reported outcomes and a measurable biological impact on inflammatory markers in a large sample size. So this is a real paradigm shift, moving CKD-aP from a symptom of uremia to some neuroimmune disorder with a targeted treatment capable of addressing both sides of the pathway.

What would you have to add about this point?

Dr. Yosipovitch:
Yes, I'd like to also mention the safety profile. In the US, there's a big concern of using any opioids because of concern about addiction. And in this case, kappa-opioids are not addictive. It doesn't cause any reward mechanism, and therefore this is not a concern at all. The safety profile is really good.

You mentioned that they do not penetrate the blood-brain barrier, but even if they do a bit penetrate, the side effect profile is very good.

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You don't have to be concerned at all about any addiction, and there's no restriction. And therefore, in patients who have so many comorbidities, it's a safe drug to use.

Dr. Lanot:
So before we wrap up, let's each offer a final take-home message. So, Gil, what do you hope our listeners will leave with today?

Dr. Yosipovitch:
So first of all, that there is a treatment that is approved both in Europe and in the US and Canada for patients with dialysis who have this pruritus that has a significant impact on quality of life. We didn't mention also that mortality-wise, patients who have pruritus have higher mortality rates. So we need to treat these patients. We have now a treatment that is effective, and this is a great message to our patients and our physicians.

Dr. Lanot:
Well, thank you. And as a nephrologist, I can only encourage all of us to adopt a proactive approach to screening for CKD-aP in our hemodialysis units, because the condition is still largely under recognized. And now that we have effective treatments that are available, our patients deserve for us to look for it systematically and to manage it properly. So my call to action is simple: ask about itch every 3 months, measure it, and treat it.

And that's all the time we have today. So I want to thank our audience for listening and thank you, Dr. Gil Yosipovitch, for joining me. I enjoyed our discussion.

Dr. Yosipovitch:
Thank you, Antoine, and goodbye.

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