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Targeting CKD-aP at the Source: Key Mechanisms and Treatments

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Dr. Fishbane:
Chronic kidney disease-associated pruritus, or CKD-aP, it's an underdiagnosed chronic condition that has significant negative impact on patients with CKD. Join us as we discuss the key mechanisms in CKD-associated pruritus pathology, new clinical practice guidelines, and emerging evidence.

This is CE on ReachMD, and I'm Dr. Steven Fishbane.

Dr. Gallieni:
And I am Maurizio Gallieni from Milano, Italy.

Dr. Fishbane:
Maurizio, let's jump in. When we start off by talking about CKD-associated pruritus, what are the definitions that you use?

Dr. Gallieni:
CKD-aP is short for chronic kidney disease-associated pruritus, and pruritus is the Latin word for itch, so we are talking about itch in patients with kidney disease. In the past, there was the term uremic pruritus, but this is no longer used, and CKD-aP is now the term that clinicians use for this old pathology with a new interest.

Recently in Europe, there was a study; I was part of that. It's called the CENSUS-EU study, where we evaluated the prevalence of patients from 7 different European countries with about 3,000 patients. And the overall prevalence of CKD-aP was 53%. And when we consider moderate to severe pruritus, this was 31%.

So, many patients at the time of this study were untreated despite experiencing itch that impacted their quality of life regarding disabilities, sleep, and depression.

Dr. Fishbane:
It's very interesting. So many patients are affected by this condition and it leads us, of course, to think about what are the causes, what is the pathogenesis? And I have to say that it's not fully known. I think we understand more about CKD-associated pruritus as time goes

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It's almost certain that part of this is related to uremic toxins. Even with the best dialysis, we're always going to have some remaining toxins in the system, and we could imagine the effect that these have both in terms of the skin, the health of the skin, and the nerves that are involved in conduction in the skin. Neuropathy is important. Both the peripheral and central nervous systems have a degree of dysfunction, which allows for a potential increase in the uptake of signals that potentially could be interpreted by the brain as related to itch.

I certainly want to note something that's become particularly important because of the availability of therapeutics now. So the effect of opioid receptors in the skin, so mu and kappa-opioid receptors, and an imbalance—and we'll come back to that because I think it's really important.

Microinflammation, so as in many diseases, we're understanding the importance of inflammation, and I didn't recognize this in the past, but I think in our discussion we'll see the importance of inflammation here. And then we get into things like cytokines and various chemokines. It's really important to also remember day-to-day items like dryness of the skin, which can be really important.

The differential diagnosis of pruritus flows naturally when we think about some of what we just discussed. So we want to know about the health of the skin. Does the skin look dry by examination? And we'd be considering the different potential causes that are involved, neuropathy, or if a patient that has an obvious lesion on the skin or a rash on the skin, that wouldn't be typical CKD-associated pruritus, but it's certainly in the same family. Often in the past, I would think about histamines and the importance of the role of histamines for different types of itch, but it's really not part of CKD-associated pruritus. So it's not something that we consider when we're treating CKD-associated pruritus.

And the drug that's available to us, difelikefalin, works specifically as a kappa-opioid agonist, so it’s working on the balance of the opioid system in the skin. And we will come back to talk more about that.

Now, why don't we shift our focus, thinking now about treatment, and, Maurizio, what are your thoughts about the standard of care for treating CKD-associated pruritus since so many patients are affected?

Dr. Gallieni:
Well, thank you, Steven, for outlining the key aspects of the pathogenesis of CKD-aP. Our extended knowledge is crucial to understand that the choice of treatment must be based on the pathogenic mechanism, and importantly, antihistamines are not a good choice when there is no histamine release. The standard of care currently reflects the fact that causes of CKD-aP are multifactorial.

So you pointed out that dry skin is one of the components, so it’s very important that our patients take care of their skin to avoid excessively dry skin, because this is a trigger for itch. But more importantly, we should go and try to identify the most relevant mechanisms that are not responding to usual treatments. And in this respect, the finding that kappa-opioid agonists can reduce itch is the most recent and relevant one.

And difelikefalin is the new drug that can be considered a standard of care. And in fact, very recently, the dermatologists, our colleagues, who are very important to us nephrologists because this is the multidisciplinary approach to this problem, provided new guidelines in Europe, the European S2K guidelines on chronic pruritus, which also includes a part on CKD-aP. And difelikefalin is recommended as one of the most relevant drugs for controlling the disease.

There are other options, in particular gabapentin and pregabalin. However, currently, because we have a safer product with the same efficacy, I think that they should be second-line treatments in cases where difelikefalin is not available. Why is that? Because the FDA recently pointed out that the use of gabapentin and pregabalin was associated with much higher risks of altered mental status, falls, and fractures.

Dr. Fishbane:
For those just tuning in, you're listening to CE on ReachMD. I'm Dr. Steven Fishbane, and here with me today is Dr. Maurizio Gallieni. We're discussing recent clinical practice guideline updates in CKD-associated pruritus.

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Dr. Gallieni:
Now that we know that difelikefalin is the recommended treatment for CKD-aP, can you tell us about the evidence behind this recommendation?

Dr. Fishbane:
Sure. Thank you, Maurizio. So difelikefalin has been studied in a number of different ways, but I think what's most important here are the pivotal phase 3 studies, two key studies that involved over 550 patients. And because itch can be a subjective symptom, it was important that these both be double-blind placebo-controlled trials, which they were. And both had a very unequivocal demonstration of the efficacy of the drug, difelikefalin, compared to placebo. And that was both in terms of the amount of itch the patients experienced, as well as measures of quality of life, which included different measures, but even sleep.

So these were very helpful studies that demonstrated the clear and unequivocal balance of excellent efficacy with a very good safety profile.

Thank you, Maurizio.

Dr. Gallieni:
I think there is another important news regarding CKD-aP, which is the possibility of identifying it with biomarkers. And this has been considered a paradigm shift in the pathophysiology and treatment of chronic kidney disease-associated pruritus. Can you tell us more about this new evidence?

Dr. Fishbane:
I do think this is fascinating and really important for clinicians. This is data from Spencer et al., and it's an interesting study. They went back and looked at the KALM studies and wanted to understand better what was the mechanism and what could they understand more with blood samples that were available. And in this case, they looked very specifically at baseline when they tried to understand the amount of itch the patient suffered from. How did markers for inflammation correlate with itch in individual patients?

This was particularly interesting because it's a study of a drug, difelikefalin, which so effectively works in the opioid system by correcting an imbalance that helps to effectively correct itch. And indeed, the drug does work that way, but in addition to that, we get new information here because the investigators in this study showed that at baseline there was a strong correlation between 10 of the key inflammatory chemokines or biomarkers that were looked at and the severity of itch in individual patients.

So simply knowing that there is an association between these chemokines in itch was important, and it suggests the fact that the inflammatory system and the presence of inflammation may play a role in terms of how itch is experienced by patients. But then they took it a step further, which I thought was really interesting. They looked at patients who responded in the studies to difelikefalin and tried to understand what happened with biomarkers.

And indeed, what they found was that as itch improved in patients, there was a significant decrease in the elevated biomarkers when they looked at 12 weeks after treatment. So itch was getting better. The biomarkers were getting better. And when they looked at people who maybe didn't have as much of a response to the drug, they found that the biomarkers didn't move to the same extent, which put a pretty sharp edge on the idea that, one, difelikefalin works through a couple of mechanisms, and one of them is an effect on inflammation, which is pretty clearly demonstrated by this data.

So pruritus, which is first picked up by nerve endings in the skin, before that sense of itch is transmitted to the brain, to the spinal cord, and then to the brain, it's modulated. There's different things that act on it. And we understand, of course, that the opiate system works here because difelikefalin has a very important effect on kappa-opioid receptors.

But there seems to be a really big interaction between inflammation and the kappa-opioid receptors here, because this anti-inflammatory effect is really an important mediator and maybe even the most important mediator in terms of why the drug is as effective as it is.

Maurizio, what did you think of this?

Dr. Gallieni:

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So having a drug that can decrease this inflammatory aspect, in addition to reducing the transmission of the sensation to the central nervous system, is actually a very powerful way of contrasting the disease.

Dr. Fishbane:
Well, our time is coming to a close. Before we wrap up, let's try to think about key take-home messages. Maurizio, what would be your one important take-home message for the audience?

Dr. Gallieni:
To go back to my observation on the prevalence of disease, I want to point out that we should look for the disease. Ask patients, because they might not tell you that they are suffering, and maybe they don't know it exactly. So it is also important to use specific methods to measure the intensity of itch of pruritus, like the Worst Itching Scale, and this will allow us to understand the real prevalence in our dialysis unit that might be greatly underestimated.

Dr. Fishbane:
And I agree so much with that statement. So many of our patients do have pruritus that they suffer from, and if we don't ask about it, we often don't find out. I guess for me, the other important take-home message would be for years I was involved with research in this area. It's a real pleasure now to have an agent, difelikefalin, that is available for treatment and really nice now to start to understand a little bit more of the science on how the drug works as broadly as it does.

And that's all the time we have today. So I want to thank our audience for listening in and thank you, Dr. Maurizio Gallieni, for joining me and sharing your thoughts with us.

Dr. Gallieni:
And thank you, Steven, for your leadership in this field and for explaining us today such important aspects of CKD-aP.

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