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Elevating CKD-aP Care: New Frontier

Announcer:
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Dr. Burton:
So this is CME on ReachMD, and welcome back, everyone. I'm Dr. Jim Burton. Here today with me is my friend and colleague, Dr. Lucio Manenti. Nice to see you, Lucio.

And today we're thinking a little bit more about the treatment of CKD-associated pruritus, and you're going to tell us a little bit about the mechanism of action of the kappa-opioid receptor agonists and maybe a summary of the agent's efficacy and safety. So over to you for that one.

Dr. Manenti:
First of all, in explaining the mechanism of action of kappa-opioid receptors, we must start from the historical fact that the use of mu-opioid agonists—for example, morphine—causes pruritus. This fact, which is very clear to anesthesiologists, has led in the past to studies investigating whether an imbalance between mu and kappa receptors could be the cause of uremic pruritus.

In fact, it has been shown that there is an imbalance between mu and kappa receptors in patients with CKD-aP, with kappa receptors playing a key role at the peripheral level—not in the central level, the peripheral level. It has therefore been demonstrated that stimulating the action of kappa receptors at the levels of peripheral pruritogenic fibers leads to a blockage of the itching signal, which does not reach the neurotransmitters in the spinal cord and therefore the brain.

This pathogenic picture has led to research into kappa-opioid receptor agonists, and difelikefalin has now demonstrated its efficacy in controlling uremic pruritus—CKD-aP. Indeed, difelikefalin is a selective opioid agonist of kappa receptors that does not cross the blood-brain barrier. And now we have the phase 3 studies leading to difelikefalin approval in the EMA and FDA agencies for use in hemodialysis patients. The studies are KALM-1 and KALM-2. Those studies demonstrated a significant reduction in pruritus versus placebo of at least 3 points on the Worst Itch Numerical Rating Scale, the scale that assesses the subjective intensity of pruritus.

In addition, there was a significant normalization of sleep, which has a tremendous impact on patients with CKD-aP, as you know.

The placebo-controlled study lasted 12 weeks, but an open-label extension phase was planned, which maintained the results for 52 weeks.

And also, the patients that received the placebo switched to the treatment arm and had a significant response in the period after the 12 weeks until the 52 weeks.

And it should be noted that these are essentially the largest studies that we have at our disposition in the treatment of CKD-aP. Every time we never had the larger studies.

But now, also, several real-world studies have been published confirming a significant reduction in pruritus in more than 50% of patients treated with difelikefalin, with no relevant side effects.

And the side effects compared to placebo were minor and mainly consisted of mild diarrhea and occasional dizziness. No new side effects were reported also in the real-world studies either.

Dr. Burton:
And so you talked about the peripheral action and the fact that it doesn't cross the blood-brain barrier. So I think I would be right in saying and we can assure the listeners that from a side effect point of view, a safety profile point of view, there's no dependence on these medications like there would be with opioids, for example, as painkillers.

Dr. Manenti:
Yes, because one of the fears when you talk about opioids is the central effects. But experimental studies on dependent people showed that there is no dependence. We knew that this drug doesn't cross the brain barrier.

Dr. Burton:
And so we have that from the studies and from the real-world evidence, so.

Dr. Manenti:
Yeah.

Dr. Burton:
Well, that's all we have time for today. Thank you very much for walking us through that, Lucio, and thanks everyone for listening, and we'll see you at the next episode.

Dr. Manenti:
Thank you. Bye.

Announcer:
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