

Difelikefalin: A Novel Therapy for Dialysis Patient Care



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People with kidney failure bear a tremendous burden of symptoms throughout their course of illness, which can profoundly shape their quality of life.¹ Pruritus is one of the most commonly reported symptoms among main-

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tenance dialysis patients² and has been prioritized as an important challenge for multiple stakeholder groups by the Standardized Outcomes in Nephrology Hemodialysis initiative.³ Treatments for pruritus that are effective in the general population offer limited relief for this population, frustrating patients and confounding their clinicians. Difelikefalin (trade name: Korsuva) promises to address this need. The drug is a novel selective κ -opioid receptor agonist that acts on peripheral sensory neurons and immune cells to modulate symptoms.⁴⁻⁷ It received US Food and Drug Administration approval in August 2021 for treatment of moderate-to-severe pruritus associated with chronic kidney disease in hemodialysis patients.

This new therapeutic option sets the stage for the articles published by Topf et al⁸ and Fishbane et al⁹ in this issue of *Kidney Medicine*. The first is a pooled analysis evaluating the effectiveness of difelikefalin among 851 participants with chronic kidney disease–associated pruritus in the KALM-1 and KALM-2 trials.^{5,10} Patients undergoing hemodialysis were randomized to receive the intravenous drug or placebo for 12 weeks followed by a year of open-label administration. Use of difelikefalin led to a greater improvement in pruritic symptoms within the first week of the trial compared with placebo, with increased effects over time in multiple subgroups. The potential for rapid and sustained symptom relief in chronic kidney disease–associated pruritus signaled by this analysis of the KALM trials is promising but does not fully address the potential for adverse events, which patients and clinicians may also weigh heavily in making treatment decisions.

The second article in this series by Fishbane et al⁹ investigates safety events in people with chronic kidney disease–associated pruritus receiving maintenance hemodialysis. This study included 4 pooled phase 3 clinical trials (the previously discussed KALM-1 and KALM-2 randomized clinical trials and the CLIN3105 and CLIN3101 open-label nonrandomized studies, which lasted 12 and 52 weeks respectively), comprising a total of 2,154 participants. Adverse events more common in those receiving difelikefalin compared with placebo included diarrhea (9.0% vs 5.7%), dizziness (6.8% vs 3.8%), nausea (6.6% vs 4.5%), gait disturbance or falls (6.6% vs 5.4%), headache (4.5% vs 2.6%), somnolence (4.2% vs 2.4%), and

mental status changes (3.3% vs 1.4%). Some of these side effects are not surprising in light of difelikefalin's known effect on opiate receptors. However, only 1 in 15 people (6.8%) receiving difelikefalin had to discontinue the drug (most commonly for dizziness) versus 1 in 25 (4.0%) of those on placebo. Discomfort and hallucinations, which are commonly associated with centrally acting κ -opioid receptor agonists, were not observed.¹¹⁻¹³ In the subset of participants in the placebo-controlled studies, 3 deaths in the difelikefalin group and the 5 deaths in the placebo group were determined to be unrelated to the study drug or protocol. Because difelikefalin has only recently become available, we do not have sufficient data regarding patient-reported symptoms in a broader nonstudy population. Going forward, it will be essential to gather additional information and evaluate patient benefit in this setting.

A novel medication that addresses major symptoms is a welcome addition to the menu of care options for patients treated by dialysis. However, this kind of innovative therapy is only beneficial if patients can access it. In the United States, recent Food and Drug Administration approval for difelikefalin was a first step in making the drug more broadly available.¹⁴ Affordability may pose another barrier. Access to novel agents can be cost-prohibitive, as pharmaceutical companies set high prices intended to recoup expenses in drug development, recognize a profit margin, and benefit company shareholders.¹⁵ At present, difelikefalin is purported to cost nearly \$2,000 per patient per month, a price that few people could afford as an out-of-pocket expense. Currently, the drug is covered by a transitional drug add-on payment adjustment for those who receive Medicare fee-for-service benefits. This mechanism became part of the end-stage renal disease prospective payment system on January 1, 2016 and allows for reimbursement of specific medications outside of the bundled payment for Medicare fee-for-service maintenance dialysis treatments.¹⁶⁻¹⁸ However, the transitional drug add-on payment adjustment typically expires 2 years after its initiation. At that time, no new funds would be available to support the added cost of this medication beyond the routine bundled payment. This would likely be unsustainable for dialysis facilities or whoever is bearing the burden of the medication cost.

Among patients who do not have Medicare fee-for-service coverage for maintenance dialysis, including those covered by Medicaid, Medicare Advantage, and commercial insurance, insurers do not automatically cover novel medications unless contractual agreements are in place with dialysis providers. Many insurers have been

slow to establish these agreements, if they are put in place at all. As more maintenance dialysis patients move away from traditional fee-for-service plans and on to Medicare Advantage plans, fewer beneficiaries will have automatic coverage under transitional drug add-on payment adjustment provisions. Legislative fixes to Medicare Advantage coverage could remedy this loophole that limits coverage of this medication for the population of patients receiving hemodialysis who are most in need.

Patients receiving peritoneal dialysis face even more substantial barriers in access to difelikefalin. An oral formulation of this medication is not yet available, and Food and Drug Administration approval currently only applies to patients receiving maintenance hemodialysis. This position is at odds with strong governmental initiatives to increase home dialysis and restricts access to a potentially important treatment for the rapidly growing population of people receiving peritoneal dialysis.

If larger future studies of difelikefalin reinforce findings from Topf et al⁸ and Fishbane et al⁹, it will be imperative upon our community of kidney professionals to advocate for improved patient access to this therapy, particularly since few therapies have recently come to market that offer improved quality of life for maintenance dialysis patients. What levers can we pull? We can work with the pharmaceutical company to advocate for reasonable pricing. We can petition Congressional leaders to establish legislation clarifying the responsibility of Medicare Advantage providers to cover these medications and ensure that the Centers for Medicare & Medicaid Services have reasonable authority and flexibility to adapt the bundled payment system. We can also actively engage the Centers for Medicare & Medicaid Services and other regulatory bodies to install mechanisms to cover future drug costs. Commercial insurers must also be included in this broader initiative.

Vulnerable patients should have access to innovations in care. This premise seems basic, but this group continues to experience barriers to access, particularly for novel and expensive therapies. As a community of kidney professionals and champions for people with kidney disease, we can gather the data needed to better understand the benefits of these therapies and use this information to advocate for improved patient care. It will take time and effort to scratch the proverbial itch on behalf of patients with chronic kidney disease-associated pruritus most in need of novel therapies like difelikefalin, but the time and effort can pay off. Not only do patients stand to benefit from improved access to this novel therapy, but learning could establish a path forward in supporting access to future novel therapies for people with kidney disease.

ARTICLE INFORMATION

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