CHRONIC KIDNEY DISEASE-ASSOCIATED PRURITUS (CKD-aP)

MEDigest

ISSUE #31: JUNE 2023

DEFINITION OF CKD-aP, PREVALENCE AND PATHOPHYSIOLOGIC MECHANISMS

In this section, we will define chronic kidney disease-associated pruritus (CKD-aP), discuss its prevalence and severity, as well as its impact on patients' quality of life and clinical outcomes. Finally, we will discuss the major hypotheses on pathophysiologic mechanisms of CKD-aP.

THE TREATMENT AND MANAGEMENT OF CKD-aP

This section will focus on currently available treatment options for managing pruritus symptoms among CKD patients. Then, we will introduce a new and the only U.S. Food and Drug Administration (FDA)-approved drug for CKD-aP, difelikefalin. Lastly, we will examine the methods and results of two significant studies: KALM-1 and KALM-2.

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FRESENIUS MEDICAL CARE

CKD-AP: EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Chronic kidney disease-associated pruritus (CKD-aP), or uremic pruritus, is defined as generalized or localized itching related to kidney disease, without another comorbid condition to explain it. It commonly occurs in dialysis patients with end-stage renal disease. The prevalence of CKD-aP reported in literature is highly variable, ranging from 18 to 80%. [1] This variability may be due to the lack of standardized tools for measuring pruritus [2], as well as low patient reporting and physician awareness. [1] The international Dialysis Outcomes and Practice Patterns Study (DOPPS) phase 5 found 17% of patients with severe constant pruritus had not reported it to their healthcare providers, and 69% of medical directors underestimated its prevalence in their units. [3] In addition, DOPPS phase 5 results reported 26%-48% of patients receiving hemodialysis (HD) experienced moderate to extreme itch. The prevalence of CKD-aP among peritoneal dialysis (PD) patients is similar to those in HD. Moderate to extreme pruritus also occurs in around 24% of non-dialysis patients. [4]

Pruritus is difficult to manage, and scratching can cause secondary skin lesions and other complications. Due to its chronic and debilitating nature, CKD-aP is associated with poor quality of life, reduced sleep quality, anxiety, and depression. Furthermore, CKD-aP is an independent predictor of hospitalization and mortality in dialysis patients. [1]

The pathophysiology of CKD-aP is not well understood. Several hypotheses exist for CKD-aP, and the mechanisms regarding the pathogenesis of it are likely to be multifactorial. [5]

One hypothesis may link **metabolic changes** and **toxin** (such as uremic toxins, Vitamin A, calcium and phosphate) **deposition** to the pathogenesis of CKD-aP. Uremic toxins might act as pruritogens that stimulate itching. Another hypothesis suggests that **immune system dysregulation** can probably contribute to CKD-aP. The progression of CKD is closely associated with systemic microinflammation, and studies have found that CKD-aP patients had high levels of inflammatory biomarkers such as T-helper 1 cells, C-reactive protein, interleukin-2, and interleukin-6. [5,6] Another hypothesis points to **neurological abnormalities**, due to the high prevalence of sensorimotor neuropathy and dysautonomia in dialysis patients. Moreover, it is hypothesized that CKD-aP is attributed to **opioid imbalance** too. Opioid receptor has been recognized as an essential modulator of itching, and opioid dysregulation such as overstimulation of central μ-opioid receptors, inhibition of peripheral κ-opioid receptors may cause itching. Finally, **xerosis (dry skin)** commonly experienced by CKD patients could be an important factor contributing to the severity of pruritus. [5]

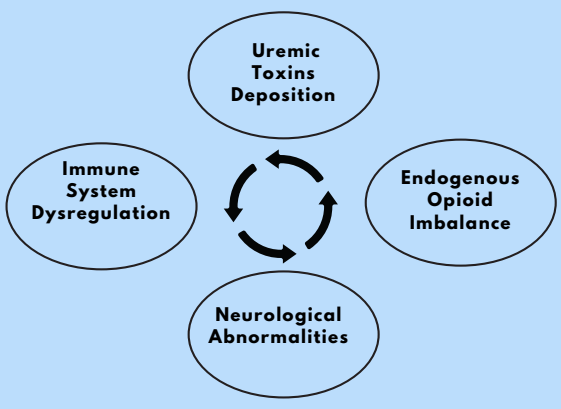

Figure 1: Pathogenic mechanisms of CKD-aP
Adapted from Kidney Int Rep 2020; 5(9):1387–1402

THE MANAGEMENT AND TREATMENT OF CKD-AP

Pathophysiological mechanisms are not fully understood, and no single treatment has demonstrated enough efficacy and safety. Treatment options can be classified into nonpharmacologic interventions, topical therapies, and systemic therapies (listed in Table 1). The treatment approach can be gradual, combining different modalities and modifying them depending on the responses of patients. [7]

Optimization of dialysis and management of metabolic parameters abnormalities, including high calcium and phosphate levels and secondary hyperparathyroidism etc., could decrease toxin deposition, thereby mitigating pruritus. Common topical treatments include emollients, analgesics, and corticosteroids. Emollients are safe and effective in reducing xerosis, while analgesics and corticosteroids might alleviate localized itching but are unsuitable for itching over large areas. Some ointments (e.g. steroids) are not recommended for long-term use. For moderate-to-severe and refractory CKD-aP, systemic therapies should be prescribed. They include neuromodulators (gabapentin and pregabalin), opioid receptor modulators, cannabinoids and antihistamines. Ultraviolet (UV) phototherapy has been used for refractory generalized pruritus and with individuals who do not desire or respond to systemic therapy. Anti-depressant sertraline also showed some efficacy in uncontrolled studies. [7]

Type	Treatment	Mechanism	Additional Description
Nonpharmacologic Interventions	Optimization of Dialysis	Improve dialysis adequacy and manage calcium, phosphorus and parathyroid hormone abnormalities	Hyperphosphatemia, hypercalcemia, and hyperparathyroidism and low Kt/VA, have been associated with increased CKD-aP severity. A few small studies found that decreasing the levels of these pruritogens may reduce itching.
	Phototherapy	Incompletely understood and a possible mechanism is immunomodulation by inhibiting T-helper-mediated immune responses and altering interleukin production [4]	Pros: effective in several noncontrolled trials; without major side-effects associated with systemic medications. Cons: low accessibility and long treatment period; potential side effect of increased risk of carcinogenesis, not recommended for immunosuppressed patients
Topical Treatments	Emollients	Improve skin hydration and repair natural protective barrier	Given its low risk of side effects, high water content emollients are recommended for all CKD-aP patients.
	Capsaicin and Pramoxine Hydrochloride	Topical analgesics by blocking the conduction of nerve impulses from the skin, leading to decreased sensation, and numbness	Generally well-tolerated Small placebo-controlled trials showed statistically significant symptom relief.
	Corticosteroids	Reduce inflammation	Very few studies on CKD-aP treatment and not intended to use in a prolonged period
Systemic Therapies	Neuromodulators: *Gabapentin and Pregabalin*	Treat peripheral neuropathy by blunting peripheral C-fiber nerve transmission and modulating the alpha-2-delta subunit of voltage-gated calcium channels	Pros: most widely studied systemic treatment in CKD-aP and of greatest importance among oral medications Cons: high risks of adverse effects; common adverse effects are drowsiness, dizziness, and somnolence.
	Difelikefalin and Nalfurafine	Opioid receptor modulation: selective κ-opioid receptor agonists	Emerging treatments μ-opioid antagonist: high risk of addiction κ-opioid agonists: no activity on μ-opioid receptor or delta-opioid receptor, thereby having low dependence, very poor blood-brain barrier penetration, and limited CNS-mediated side effects Nalfurafine was approved in Japan (2009) and South Korea (2013).
	Naltrexone	Opioid receptor modulation: μ-opioid receptor antagonists	
	Nalbuphine and Butorphanol	Opioid receptor modulation: combined μ-opioid receptor antagonists and κ-opioid receptor agonists	
	Cannabinoids	Activation of cannabinoid-1 receptor and cannabinoid-2 receptor in cutaneous nerve fiber bundles are found to attenuate axonal response.	Research on cannabinoids is growing. Though cannabinoids have been shown to be successful in other pruritic conditions, such as cholestatic itch, there are very limited evidence on CKD-aP treatment by far.
	Antihistamines	Histamine and tryptase are mast cell mediators and itch elicitors. Current treatments are divided into histamine receptor antagonists and mast cell stabilizers. [4]	It is commonly applied to treat pruritus. However, antihistamines have displayed limited efficacy in the treatment of CKD-aP. In addition, sedation is one of the common side effects and could increase the risk of fall in elderly.

Table 1: Common CKD-aP treatments, mechanisms, and additional descriptions.
Compilation of information from Clin Kidney J 2021; (14)3:16-22 and Kidney Int Rep. 2020; 5(9):1387–1402 for clarity.

COMPANY INITIATIVES

Double-blind, randomized placebo-controlled phase 3 KALM-1 and KALM-2 trials on Difelikefalin

A few years ago, Vifor Pharma, Cara Therapeutics and Fresenius Medical Care entered a partnership to use difelikefalin (DFK), a novel selective κ-opioid receptor agonist, for the treatment of CKD-aP. In August 2021, DFK was approved by the U.S. FDA and in April 2022 by European Medicines Agency as the first drug for the treatment of moderate to severe CKD-aP in adult hemodialysis patients.

The approval was based on two pivotal phase-3 trials: KALM-1 trial (56 sites in the U.S.) and KALM-2 trial (75 sites in the U.S., Europe, and Asia). Patients' itching severity was measured using the Worst Itching Intensity Numerical Rating Scale (WI-NRS) (Figure 1). At least 3 points reduction in WI-NRS represented a clinically meaningful improvement in itch intensity in previous phase 2 trials, which was continuously the primary outcome measure in phase 3. Secondary efficacy outcome measures were at least 4 points reduction in WI-NRS and itch-related quality of life. DFK (0.5 μg/kg of body weight) or placebo was administered intravenously 3 times/wk for 12 weeks. The patients then entered a 2-week discontinuation period to monitor withdrawal symptoms, followed by a 52-week open-label extension phase to further evaluate the safety. [8]

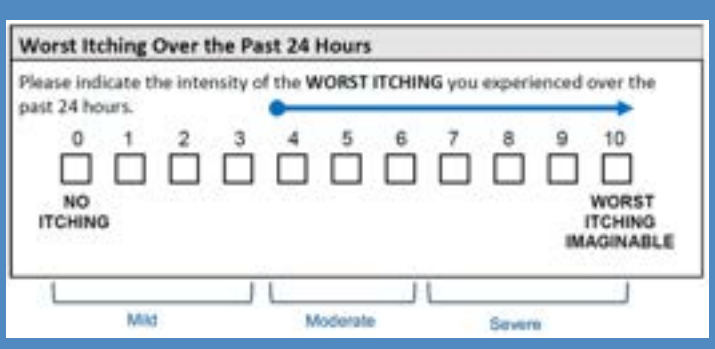

Figure 2: WI-NRS: Worst Itching Intensity Numerical Rating Scale.
Adapted from Lipman M. et al, 2021; 14(3):16–22.

The KALM-1 phase 3 results showed a significantly greater WI-NRS decrease of ≥ 3 points in the DFK group compared with the placebo (49.1% vs. 27.9%; RR: 1.65; 95% CI: 1.26 to 2.14; P<0.001). Similarly, a higher percentage of patients in the DFK group than in the placebo group had a decrease of ≥ 4 points in WI-NRS (37.1% vs. 17.9%; RR: 2.70; P<0.001). DFK also improved itch-related quality of life as measured by the 5-D itch and the Skindex-10 questionnaires (37.1% vs. 17.9%, P<0.001) from baseline to week 12. Adverse events of diarrhea (8.1% vs. 5.5%), dizziness (5.5% vs. 5.1%), and nausea (6.4% vs. 4.2%) were more frequent in the DFK group than placebo. [8]

Results from KALM-2 phase 3 demonstrated consistent efficacy of DFK in CKD-aP relief among HD patients, as reported by KALM-1. [9] Pooled analysis of KALM-1 and KALM-2 phase 3 trials (DFK, n=426; placebo, n=425) showed a significantly greater proportion of ≥3-point WI-NRS reduction in DFK than placebo groups (51.1% vs 35.2% P < 0.001). [10]

It should be noted that though KALM-1 and KALM-2 demonstrated efficacy on CKD-aP itching intensity reduction, the trials only enrolled adult patients undergoing HD. [9] Therefore, further clinical trials might continue to study the treatment effect of DFK in other subgroups and comparisons with other treatment options.

References: (1) Kim D, et al. Clinical Kidney Journal. 2021;14(3): 1-7; (2) Hu X, et al. Medicine. 2018; 97(21):e10633; (3) Rayner H, et al. Clin J Am Soc Nephrol. 2017; 12:2000-2007; (4) Sukul N, et al. Clin J Am Soc Nephrol. 2019;14: 673–681; (5) Verduzco HA, et al. Kidney Int Rep. 2020; 5(9):1387–1402; (6) Schricker S, et al. Clinical Kidney Journal. 2021;14(3):23–31. (7) Lipman ZM, et al. Clinical Kidney Journal. 2021; 14(3):16–22; (8) Fishbane S, et al. N Engl J Med. 2020; 382(3): 222–232; (9) https://www.asn-online.org/education/kidneyweek/2020/program-abstract.aspx?controlId=3444152;[Accessed 23 Mar 2023]; (10) Topf J, et al. Kidney Med. 2022;4(8):100512.