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REVIEW

Identification and Management of CKD-Associated Pruritus: Current Insights

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Abstract: Chronic kidney disease-associated pruritus (CKD-aP) is a frequent and distressing problem for individuals with chronic kidney disease (CKD) and end-stage renal disease. It affects around 20% of those with CKD and 40% of those with end-stage renal disease. Despite its clear association with poorer psychosocial and medical outcomes, it is often underreported by patients and frequently remains unnoticed by healthcare providers. This is likely due to uncertainty regarding its diagnosis and treatment. Most commonly, CKD-aP could be screened with questionnaires like the KDQoL-36 and WI-NRS, chosen for their simplicity and ease of use. Prior treatment studies of CKD-aP were mostly limited by noncontrolled design and small sample size. First CKD-aP medication – difelikefalin a powerful, new therapeutic option was approved by Federal Drug Administration (FDA) in 2021 and European Medicines Agency (EMA) in 2022. Recent expert opinions, clinical trials and metanalysis identified difelikefalin and gabapentinoids as medications of choice in treatment of CKD-aP. All these findings improved current understanding and management of this condition.

Keywords: difelikefalin, chronic kidney disease, itch, pruritus, pregabalin, gabapentin

Introduction

Among the various systemic disorders associated with itching, chronic kidney disease (CKD) requires particular attention.[1] Defined in 2002 by the National Kidney Foundation, CKD is characterized by structural or functional abnormalities of the kidneys that persist for at least three months, with significant implications for a patient's health.[2] The prevalence of CKD is around 13%, making it a major public health concern.[3,4] CKD is associated with numerous complications, many of which involve the skin.[5] Common dermatological manifestations in end-stage renal disease (ESRD) include changes in skin color, elastosis, bruising, dry skin (xerosis), uremic frost, acquired perforating disorders, metastatic calcification, and bullous dermatosis of hemodialysis.[1,5] One of the most prevalent and distressing skin symptoms in dialysis patients, first documented in 1932, is CKD-associated pruritus (CKD-aP).[1] The terminology for this condition evolved over time; while it was once called "uremic pruritus", the term CKD-aP or "CKD-associated itch" is now preferred due to the lack of direct correlation between uremia and itching.[6] This condition not only worsens sleep, mood, daily activities, and overall quality of life (QoL) but also elevates the mortality risk for patients undergoing hemodialysis (HD).[7,8]

The clinical presentation of CKD-aP is highly variable, making diagnosis and treatment challenging.[9,10] Currently, there is a scare number of up-to-date guidelines established for managing CKD-aP in dialyzed patients.[11–13] The limited number of guidelines for its diagnosis and management leads to under-diagnosis and suboptimal treatment approaches.[10,12,13] European Medicines Agency (EMA) and Federal Drug Administration (FDA) approved difelikefalin, the first drug specifically indicated for CKD-aP in dialyzed patients, which demonstrated efficacy in two Phase 3 clinical trials.[14] The development of this targeted medication, supported by solid evidence of its effectiveness and safety, increased awareness and understanding of this condition.[11] According to the most current expert recommendations, difelikefalin should be first-line medication for patients with moderate-to-severe CKD-aP undergoing dialysis.[13] Other therapies should only be considered as first-line choice for those patients only if difelikefalin is not available.[13] Although,

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difelikefalin showed promise as a treatment for CKD-aP in dialyzed patients, particularly through its selective κ-opioid receptor agonist activity, the current body of evidence has limitations. Several studies, including the pivotal KALM-1 and KALM-2 trials, demonstrated significant efficacy in reducing itch intensity and improving quality of life in hemodialysed patients.[14] However, these studies were conducted in relatively controlled settings and focused predominantly on specific patient subsets, primarily those undergoing dialysis.

A notable gap remains in the form of large-scale, multicenter randomized controlled trials (RCTs) with diverse CKD populations, including those not on dialysis or with varying comorbidities. Additionally, long-term safety and efficacy data for difelikefalin are still emerging, highlighting the need for extended follow-up studies to assess sustained benefits and potential risks.

Addressing this gap with well-powered trials would not only validate the utility of difelikefalin across broader patient populations but also facilitate a deeper understanding of its comparative effectiveness against other pruritus management strategies. This need underscores an essential area for future research, particularly as CKD-aP remains a significant unmet need impacting patient well-being and treatment adherence. This narrative review aims to provide updated insights into the diagnostic and therapeutic management of dialyzed CKD-aP patients.

Epidemiology

Prevalence

The prevalence of CKD-aP among adult patients with ESRD decreased due to improvements in dialysis.[6] While prevalence rates ranged from 50 to 90% between 1980 and 1993,[15,16] more recent studies reported lower rates, between 22% and 57%.[17–20] A prospective cohort study, the Dialysis Outcomes and Practice Patterns Study (DOPPS), which included over 20,000 hemodialysis patients, found that 37% experienced at least moderate pruritus consistently from 2009 to 2018, with 7% of participants being severely affected by pruritus.[21] Pruritus often goes unreported by patients and underestimated by healthcare providers.[19,21] Among DOPPS participants with severe pruritus, 18% did not receive treatment, and 17% did not disclose their symptoms to medical staff.[19,21] Additionally, more than two-thirds of medical directors underestimated the prevalence of pruritus in their facilities.[19,21]

Although research on the prevalence of pruritus among patients on peritoneal dialysis and children is limited, a cross-sectional study revealed that approximately 20% of children with CKD had CKD-aP (18% of non-HD and 24% of those on HD).[21–24] Earlier studies suggested that the prevalence in children is lower (around 9%) and similar between patients on hemodialysis and peritoneal dialysis.[21–23] However, two studies from Korea and Taiwan revealed differing results.[25,26] The Korean study found higher pruritus rates in patients on peritoneal dialysis (68.2%) compared to hemodialysis (48.3%), but the Taiwanese study found no significant difference between the two groups.[25,26]

CKD-aP is less frequent in patients with no-dialysis CKD.[27] A study involving over 5,600 patients with stages 3, 4, and 5 no-dialysis CKD reported that 24% had at least moderate pruritus, and less than 5% experienced extreme pruritus.[27] The prevalence and severity of pruritus increased with the progression of CKD stages.[27]

Risk Factors

No single cause of CKD-aP was identified, but various factors were associated with its occurrence in observational studies.[1] Treatments often target these factors.[1] Dysregulation between μ-opioid and κ-opioid receptor activity plays a critical role in modulating itch sensations. Specifically, reduced μ-opioid receptor activity and heightened κ-opioid receptor signaling are crucial in pruritus pathogenesis.[28] Current treatments, such as difelikefalin, support this understanding by selectively targeting peripheral κ-opioid receptors, thereby reducing itch intensity without central nervous system effects.[28] Other notable risk factors, which were suggested including:

- Inadequate dialysis[17,29,30]
- Hyperparathyroidism[31–33]
- High levels of serum calcium or phosphorus[31,34,35]
- Xerosis (dry skin from sweat gland atrophy)[36,37]

- Elevated serum magnesium and aluminum levels[38–40]
- Peripheral neuropathy[28,41,42]
- Microinflammation[13,43]

However, some studies did not find a consistent association between high parathyroid hormone or phosphorus levels and pruritus.[23,44] Other potential risk factors include anemia, male sex, hypervitaminosis-A, increased beta-2 microglobulin, certain human leukocyte antigen (HLA) types, and comorbid conditions like congestive heart failure, and ascites.[19,35,45–47] The risk of pruritus appears independent of ethnicity, dialysis type, and the underlying kidney condition.[6]

Pathophysiology of CKD-aP

The exact pathophysiology of CKD-aP remains incompletely understood, but emerging evidence highlights metabolic, immunological, and neurological factors.[9,28]

In CKD, the accumulation of uremic toxins, such as indoxyl sulfate and p-cresyl sulfate, contributes to systemic inflammation and neurotoxicity.[9,28] These toxins can sensitize peripheral and central nervous systems, amplifying itch perception.[9,28] Dysregulated calcium-phosphate metabolism, hyperparathyroidism, and increased phosphorus levels found in pruritus, potentially influence on skin homeostasis and nerve excitability.[9,28]

CKD-aP is increasingly recognized as an inflammatory condition.[27,44] Elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-31 (IL-31), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) are frequently observed in CKD patients with pruritus.[27,44] IL-31 plays a significant role in promoting itch through its receptor, expressed on sensory neurons and keratinocytes.[27,44] Dysregulation of Th1/Th2 cytokine balance and increased activation of mast cells further exacerbate skin inflammation and pruritus.[27,44]

Neurological disturbances in CKD-aP involve both peripheral and central pathways.[8,10] Peripheral sensory neurons, particularly C-fibers, become hypersensitive to pruritogenic stimuli due to chronic inflammation and metabolic imbalances.[8,10] At the central level, imbalance in the opioid system plays a critical role.[8,10] An imbalance between μ-opioid receptor activation (which suppresses itch) and κ-opioid receptor activity (which promotes itch) was noted in CKD-aP patients.[8,10] This imbalance could result from the reduced expression of μ-opioid receptors or increased κ-opioid activity, both of which are influenced by the uremic environment.[8,10]

Although CKD-aP is not only a dermatological condition, changes in skin integrity also contribute significantly to its presentation.[48,49] Xerosis (dry skin) is prevalent in CKD and exacerbates itch.[48,49] Reduced hydration, altered lipid composition, and impaired barrier proteins (eg, filaggrin) compromise the skin's defense, allowing pruritogens to penetrate more easily and stimulate sensory nerves.[48,49]

Endogenous pruritogens, such as histamine, serotonin, and proteases, play diverse roles in CKD-aP.[48,49] While histamine-independent pathways are predominant, histamine could still contribute via mast cell degranulation.[48,49] Other mediators, such as bile acids and lysophosphatidic acid (LPA), are thought to activate specific receptors (eg, TGR5 and LPARs) on sensory neurons, leading to itch sensation.[48,49] Elevated β-endorphins and dynorphins in CKD patients also interact with opioid receptors, further modulating pruritus.[48,49]

Diagnosis

Clinical Characteristic

CKD-aP most often affects the back but can also impact the arms, forearms with arteriovenous shunts, head, and abdomen, with many patients experiencing generalized itching.[19,50] The intensity varies: some patients experience brief episodes each day, others suffer from near-continuous itching.[51]

Other characteristics of CKD-aP include:

- Symptoms typically worsen at night, leading to sleep disturbances.[19,20,50–52] This problem is more severe in patients with intense pruritus, often causing fatigue and depression.[19,21,23]

- Pruritus tends to increase with heat, especially with excessive sweating, and stress.[6] It may decrease with physical activity, cooler temperatures, and either hot or cold showers.[6]
- Some patients experience worsening of pruritus during hemodialysis sessions, while others find relief during these sessions.[34,50]

Physical examination usually shows minimal findings unless there are additional skin conditions caused by scratching, such as excoriations, lichen simplex, prurigo nodularis, keratotic papules, or follicular hyperkeratosis.[16] Xerosis (dry skin) is common in those with CKD-aP, though it might only become apparent upon close inspection, showing skin scaling and cracking.[53]

Laboratory findings in patients with pruritus can include elevated levels of blood urea nitrogen (BUN), parathyroid hormone (PTH), phosphate, calcium, and magnesium compared to those without pruritus.[17] A study involving 1,773 adult hemodialysis patients found that those with severe pruritus were more likely to have BUN levels >81 mg/dL, calcium >9.5 mg/dL, phosphate >6.6 mg/dL, and less likely to have a PTH level <200 pg/mL.[17] Although laboratory abnormalities could be observed, there are no reliable markers established for patients with CKD-aP.[13]

Screening

Pruritus in CKD patients is often assessed using questionnaires, like the The Kidney Disease Quality of Life 36-item short-form survey (KDQoL-36) and Worst Itch Numeric Rating Scale (WI-NRS), chosen for their simplicity and ease of use.[54–56] Initial screening for chronic pruritus focuses on a specific question (question 20) of the KDQoL-36, which asks about discomfort due to itching over the past 4 weeks, with responses ranging from "none" to "very much".[54] This screening is typically done by nephrologists or nursing staff every three months for patients without a CKD-aP diagnosis.[54] If a patient reports significant discomfort, a more thorough differential diagnosis is conducted to rule out other potential causes.[54] WI-NRS is a simple-to-use, single-item, monodimensional patient-related outcome.[57] Patients indicate the intensity of the worst itching they have experienced over the past 24 h by marking one of 11 numbers—from 0 to 10—that best describe the worst itching experiences ('0' labeled with the anchor phrase 'no itching' and '10' labelled 'worst itching imaginable').[57] This WI-NRS was validated for multiple dermatologic conditions, including CKD-aP.[57–59] After identifying potential CKD-aP patients, pruritus severity is assessed using the WI-NRS.[11,52,53] WI-NRS $\geq 3 < 4$ corresponds to mild, WI-NRS $\geq 4 < 7$ to moderate and WI-NRS ≥ 7 to severe intensity of itching, Table 1.[11] Apart from WI-NRS and KDQoL-36 in the clinical trials multiple scales that assess impact of itch on quality of life are utilized. For example, the Skindex-10 is a dermatology-specific instrument designed to measure the emotional, functional, and symptomatic burden of skin conditions, including pruritus.[60] The 5-D Itch Scale (duration, degree, direction, disability, and distribution) is another valuable tool that captures the multidimensional aspects of pruritus.[61] Incorporating these scales into clinical assessments provides a more comprehensive understanding of how pruritus affects patients' daily lives and facilitates standardized comparisons of treatment efficacy across studies.[60]

Differential Diagnosis

The differential diagnosis process involves evaluation for skin lesions, which may be primary or secondary[12] Figure 1. Primary lesions are not associated with CKD-aP, whereas secondary ones could be.[12] A thorough skin examination, ideally done in a private consultation room, is needed.[12] If primary lesions are found, these are diagnosed and treated by a dermatologist.[12] In the absence of primary lesions, other possible causes of pruritus, such as hematological, liver,

Table 1 Assessment of the Intensity of Itching

WI-NRS Questionnaire Score	Intensity of Itching
NRS = 0	No
NRS ≥ 3	Mild
NRS ≥ 4 < 7	Moderate
NRS ≥ 7	Severe

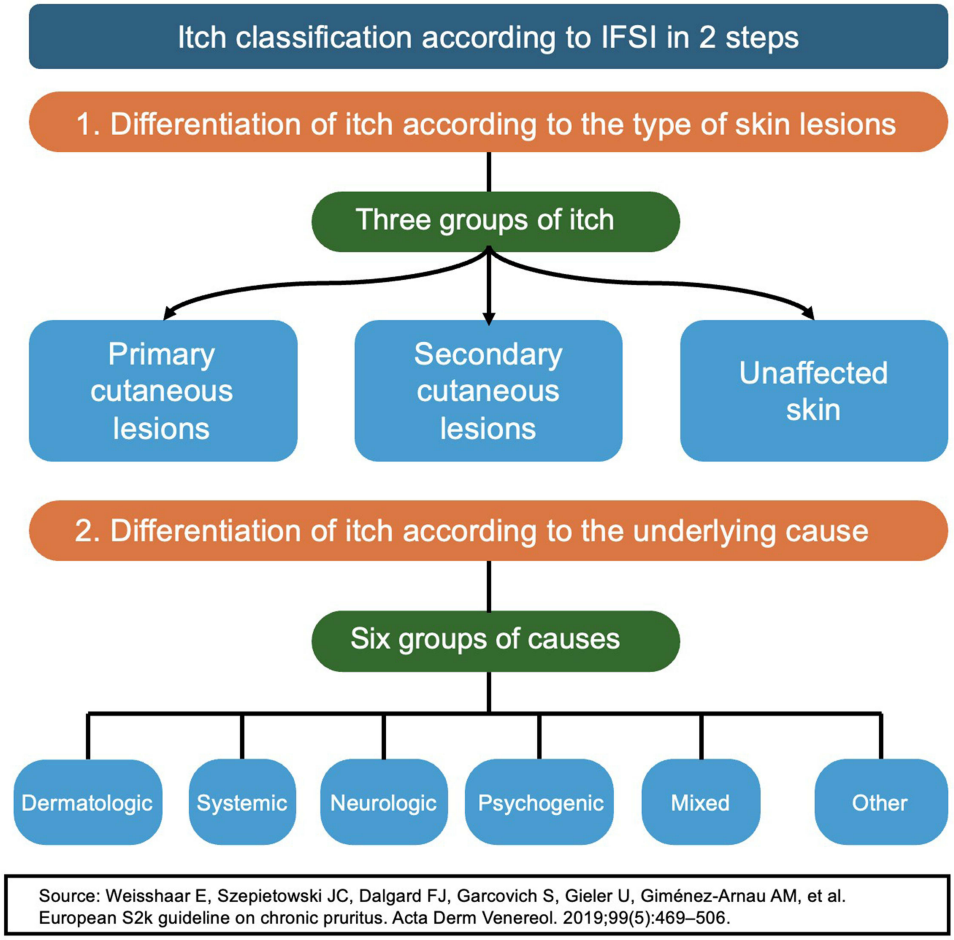

Figure 1 Itch classification according to International Forum for the Study of Itch (IFSI).

neurological, or psychiatric conditions, as well as certain medications or malignancies, should be ruled out.[11,12] Patients are then referred to the appropriate specialist for further treatment if another cause is identified.[11,12] CKD-aP is diagnosed if no other cause is found, though xerosis could coexist with CKD-aP despite being a primary skin condition.[11,12]

Management

The treatment of CKD-aP follows a stepwise approach, tailored to symptom severity and patient response to each stage of therapy.[10,62–65] Given the scarcity of high-quality evidence, most recommendations originate from anecdotal experiences and small-scale, observational studies.[10,62–65] The interpretation of available studies is further complicated by varying scoring systems for pruritus severity and a lack of direct comparisons between treatments.[10,62–65] Additionally, some studied treatments could not be commercially accessible, and the placebo effect was notably stronger in many trials.[10,62–65] Most research was focused on hemodialysis patients, leaving limited data for those on peritoneal dialysis or with non-dialysis CKD.[10,62–65]

Baseline treatment of all CKD-aP patients rely on three therapeutic pillars:

Optimal Dialysis

Ensuring adequate dialysis is critical, as underdialysis is often linked to pruritus.[29,30,66] For patients on dialysis, adjusting the dialysis dose or membrane type can help reduce itching.[29,30,66] For those with non-dialysis CKD, chronic dialysis is not typically initiated solely to manage pruritus.[29,30,66] Adjusting dialysis parameters, such as the Kt/V values (a measure of dialysis adequacy), could improve pruritus.[29,30,66] Some studies suggested that increasing the dose of dialysis could

reduce itching, although results are inconclusive.[29,35] For example, a 1995 study found that patients receiving a higher dose of dialysis reported less pruritus.[29] However, other studies yielded conflicting results, indicating that factors like contact with dialysis equipment or other underlying conditions could influence pruritus.[35,66,67] Switching from bioincompatible or low-flux membranes to biocompatible, high-flux ones might decrease pruritus in certain patients.[68–70] For instance, studies indicate that patients who transitioned to membranes made with materials like polymethylmethacrylate (PMMA) experienced reduced itching.[68–70]

Managing Hyperparathyroidism and Hyperphosphatemia

Proper control of these conditions is essential for managing CKD-aP.[13,34,35] Treatment goals on maintaining targeted levels of parathyroid hormone (PTH) and phosphate, although specific values for controlling CKD-aP were not established.[13,34,35] Controlling PTH levels is important as elevated levels could lead to secondary hyperparathyroidism, a common complication in CKD that contributes to itching.[13,34,35] Similarly, managing serum phosphate levels is critical because hyperphosphatemia was associated with increased skin deposition of calcium-phosphate crystals, which might exacerbate pruritus.[13,34,35] Maintaining balanced PTH and phosphate levels through appropriate medication, dietary restrictions, and dialysis adjustments is one of key strategies in the comprehensive management of CKD-aP.[13,34,35]

Emollients

Applying emollients is recommended, especially for patients with dry skin, to help alleviate symptoms. Emollients that have a high-water content are preferred.[71] Since xerosis is common and could be challenging to detect, emollient therapy should be used even for patients without visible signs of xerosis. Typically, patients administer an emollient for a minimum of two weeks to assess its effectiveness before considering other medical treatments.[71] However, in adequately dialyzed patients with severe pruritus, additional therapy should not be delayed.[71] Patients continue to use emollients indefinitely, regardless of the initial response, as insufficiently treated xerosis could hinder the effectiveness of other treatments.[71]

Balaskas et al[70] conducted a randomized, double-blind study involving 99 patients with uremic xerosis, treated with an oil-in-water emulsion containing 15% glycerol and 10% paraffin. Itch levels were assessed using a 100-mm Visual Analog Scale (VAS), starting at a baseline of 40.64 ± 3.36 mm.[72] By days 28 and 56, there was a significant reduction in itch scores, measuring 13.39 ± 2.19 mm and 10.66 ± 2.14 mm, respectively.[72] On day 56, there was also notable improvement in quality of life (QoL) based on the DLQI and SF-12 questionnaires.[72] In the recent three periods study, this topical agent was evaluated on 235 dialysis patients with CKD and uremic xerosis.[73] The first one was double blind RCT in which patients with moderate-to-severe uremic xerosis were randomized to once-daily application of the lotion or vehicle control for 28 days.[73] This was followed by a treatment-free period ≤21 days (period II), then all patients received open-label treatment with lotion for ≥84 days.[73] Mean ± SEM pruritus VAS scores were comparable between the lotion (16.9 ± 2.2) and vehicle control groups (15.1 ± 2.0) at the end of period I.[73] After a slight rebound during period II and up to the start of period III (20.2 ± 2.7 vs 19.3 ± 2.5 mm), pruritus was significantly decreased in both groups through to the end of period III (10.4 ± 1.9 vs 7.5 ± 1.4 mm).[73] DLQI scores showed a significant reduction versus baseline at the end of period I and II in both groups, what indicated an improvement in QoL.[73] Although no additional antipruritic benefit of glycerol and paraffin was shown, the main antipruritic effect of this product could be caused by its oil-in-water emulsion base.[73] Significant improvements in DLQI scores in both groups suggested that relief of pruritus is an important determinant of QoL in patients with uremic xerosis.[73]

Previous study explored the potential of endocannabinoids in managing ESRD-associated chronic itch (ESRDCI), proposing that these compounds could alleviate itching through mechanisms which include histamine reduction, vasodilation, and downregulation of mast cells (MCs).[74] Thirty-one ESRDCI patients undergoing HD were treated with a cream containing structural physiologic lipids and endogenous cannabinoids, applied twice daily for three weeks.[74] Of these, 21 patients were included in the final analysis. The baseline itch intensity, measured with a Visual Analog Scale (VAS), was 6.24 ± 2.19.[74] After 21 days of therapy, the score significantly decreased to 1.29 ± 1.41.[74] At a follow-up visit, conducted 14 days after discontinuing the therapy, itch levels increased to 2.43 ± 2.82 (P = 0.02), but

the values remained significantly lower than the baseline ($P < 0.001$).[74] Additionally, more than 90% of patients considered the therapy to be at least "satisfactory".[74]

It was also reported that balneological therapy using polidocanol in bath oil could be successful for ESRDCI patients on HD.[62] Thirty-one patients received 150-L baths with 30 mL of polidocanol every two days, each lasting 10 to 15 minutes.[62] After four weeks, 87% of patients experienced complete relief from itching, with 10% showing marked improvement, and 3% reporting moderate improvement.[62]

Several randomized, double-blind, placebo-controlled studies tested emollients for CKD-aP including gamma-linolenic acid 2.2% cream and sericin cream, all of which showed statistically significant effects in treated patients.[75,76]

For patients who do not respond sufficiently to emollients, more targeted therapies could be introduced one by one.

Topical Analgesics

For patients with mild CKD-aP who continue to experience symptoms despite using a skin moisturizer, a topical analgesic could be recommended. These should be applied to the specific areas of itching and discontinued if no improvement is seen after about one week.[77] Preferred topical analgesic could be lotion containing 1% pramoxine hydrochloride, which is available over the counter and generally safe.[77] In a randomized study involving 28 hemodialysis patients, using pramoxine twice daily significantly reduced itching compared to a vehicle (61% vs 12%).[77] Topical NSAIDs or capsaicin should not be recommended for patients with CKD-aP.[78–80] Topical NSAIDs were not evaluated for this condition and could negatively impact residual kidney function.[78–80] Although capsaicin showed some effectiveness for localized itching,[78–80] it often causes an uncomfortable burning or stinging sensation. Additionally, the design of existing capsaicin studies has limitations that make the results difficult to interpret.[81]

Phototherapy

Phototherapy using narrow – band ultraviolet B (UVB) irradiation could be proposed for moderate-to-severe CKD-aP as a next step in the therapeutic ladder. However, it carries risks, such as increased cancer risk, especially in patients on immunosuppressive therapy.[82] Narrow band UVB is not recommended for patients with conditions like lupus erythematosus due to photosensitivity.[82] The positive effects of UVB therapy are believed to result from a reduction in proinflammatory cytokine levels and the promotion of mast cell apoptosis.[83] UVB irradiation could be effective for treating CKD-aP, as indicated by findings from small or uncontrolled studies.[48,84–87] For instance, in one study, 8 out of 10 patients with persistent pruritus experienced symptom relief after undergoing UVB therapy.[85] The treatment started with a UVB dose of 200 to 400 mJ/cm², increasing by 100 mJ/cm² with each session, up to a maximum of 1500 mJ/cm² per session.[85] However, the return of symptoms after stopping the therapy could be a concern.[85] In this study, four patients who initially responded experienced a recurrence of symptoms.[85] Patients with CKD-aP should be irradiated at least 2–3 times a week to get a satisfactory outcome.[88] Most of the UVB therapy centers are localized in the tertiary clinics.[88] Number of the phototherapy centers is limited and scare in rural areas.[88] All these severely limits the usefulness of UVB therapy in CKD-aP patients.[88]

Difelikefalin

According to recent expert recommendations difelikefalin, a highly selective agonist of the κ-opioid receptor, should be administered as a first-line treatment for moderate-to-severe CKD-aP.[11,13] Difelikefalin was approved by FDA in 2021 and by EMA in 2022 as the first medication specifically for CKD-aP.[11] Its effectiveness in treating CKD-aP was demonstrated through two Phase 3 clinical trials (KALM-1 and KALM-2), each lasting 12 weeks, as well as an additional 52-week open-label extension study involving hemodialysis patients.[14] The reduction in the intensity of itching resulted in significant long-term improvements in patients' health-related quality of life (HRQoL), as seen in KALM-1 and its open-label extension phase.[14] In both KALM-1 and KALM-2, a significantly larger percentage of patients treated with difelikefalin showed an improvement of at least 3 points on the WI-NRS scale compared to those who received a placebo.[14] During the double-blind phase, those in the difelikefalin group continued to experience improvements in both pruritus severity and HRQoL (as measured by the 5-D Itch Scale and Skindex-10).[14] Additionally, patients who initially received a placebo during the double-blind phase and later switched to difelikefalin in the KALM-1

open-label extension showed an average improvement of 6.9 points (95% CI −7.7 to −6.2) on the 5-D Itch Scale from the start to week 52 of the extension phase.[14]

Difelikefalin is administered three times a week via a quick intravenous injection into the venous line of the dialysis circuit at the end of a hemodialysis session, either during or after returning the blood to the patient.[11] This method of administration ensures that difelikefalin does not require additional visits, making it convenient and potentially improving patient adherence.[11] Furthermore, it does not require extra monitoring, which simplifies its use. The recommended dose is 0.5 μg/kg of the patient's dry body weight (the target weight after dialysis).[11]

Gabapentinoids

If difelikefalin is not available, for patients with moderate-to-severe CKD-aP gabapentin or pregabalin could be recommended as first-line treatment.[62] If there is no improvement after four to 6 weeks, the medication should be stopped.[62] The starting dose for gabapentin is 100 mg after each dialysis session, and this can be gradually increased to 300 mg daily depending on the response.[62] Pregabalin is initially prescribed at 25 mg daily, which can be increased to 75 mg daily if needed.[62] Doses higher than 300 mg per day for gabapentin and 75 mg per day for pregabalin are not advised for patients with stage 5 CKD, whether on dialysis or not.[62] Patients using these medications should be monitored for potential side effects, such as dizziness and drowsiness.[62]

Gabapentinoids are often used for various neuropathic pain conditions and showed effectiveness in treating CKD-aP in several smaller studies.[89–97] A meta-analysis of randomized trials, which included five studies with a total of 297 CKD-aP patients, found that treatment with gabapentin or pregabalin reduced itching by about five points on a 11-point visual analog scale.[98]

There are several therapies for CKD-aP of limited use, which could be found in available literature. Some of they are discussed below:

Opioid Receptor Agonists and Antagonists

Nalbuphine

Another opioid used in patients with moderate-to-severe CKD-aP with satisfactory outcomes is nalbuphine.[1,63] This drug acts as a mixed κ-agonist and μ-antagonist opioid modulator.[1,63] In a large, multicenter, randomized, double-blind, placebo-controlled study, 373 patients undergoing HD received extended-release nalbuphine tablets (either 60 mg or 120 mg) or a placebo over a period of 8 weeks.[1,63] The 120 mg group experienced a significant reduction in itch severity compared to the placebo group.[1,63] Additionally, this dose led to a significant improvement in sleep disturbances caused by itching compared to placebo.[1,63] However, the tolerance for nalbuphine was low, with a high dropout rate of about 25% in the treatment groups compared to the placebo group.[63] In a separate open-label study with 15 hemodialysis patients suffering from pruritus, a dose-escalation trial of nalbuphine showed a decrease in the mean visual analog scale score from 4 to 1.2 points at a dose of 180 mg/day and to 0.4 points at 240 mg/day.[99] The results suggested that nalbuphine administered as tablets was safe and well tolerated in HD patients.[99] It could be effective in reducing pruritus in HD patients, with particular benefit at doses of 60 mg or higher.[99]

Butorphanol

Butorphanol showed promise for use in outpatient dermatology due to its effectiveness, ease of use, and generally favorable side effect profile.[100] In series of patients, intranasal butorphanol proved to be highly effective in managing severe, treatment-resistant pruritus.[100] It remains uncertain whether butorphanol is effective for all types of pruritus, particularly CKD-aP.[100] Further research through a large, prospective clinical trial would be valuable to assess its effectiveness.[100]

Nalfurafine

Nalfurafine, a kappa-opioid receptor agonist, was proved to be effective in treating CKD-aP.[101,102] According to a meta-analysis of randomized controlled trials (RCTs), nalfurafine significantly reduced itching in 144 hD patients compared to a placebo over 2 and 4 weeks.[102] In a separate 2-week study involving 337 hD patients with pruritus, randomized into three groups (1:1:1) receiving either 5 mg of nalfurafine, 2.5 mg of nalfurafine, or a placebo, both doses of nalfurafine

(5 mg and 2.5 mg) led to a significant reduction in itching.[102] Currently, oral nalfurafine is approved for the treatment of resistant pruritus in HD patients only in Japan.[103] A key distinction between nalfurafine and difelikefalin is in their mechanism of action and site of activity. Nalfurafine is a centrally acting κ-opioid receptor agonist, which crosses the blood–brain barrier acts on central nervous system (CNS).[104] This central mechanism is thought to modulate itch perception and reduce pruritus severity.[104] In contrast, difelikefalin is a peripherally acting κ-opioid receptor agonist that does not cross the blood–brain barrier, focusing its action on peripheral nerve terminals and immune cells.[104] This distinction is clinically significant as it could account for differences in efficacy, safety profiles, and side effects, with nalfurafine having potential CNS-related side effects like sedation and dizziness, while difelikefalin is less likely to cause such central effects.[104]

Naltrexone

The effectiveness of the μ-receptor antagonist naltrexone in treating CKD-aP showed inconsistent results across studies.[1] In one study, a dose of 50 mg/day of naltrexone taken orally for 7 days significantly reduced CKD-aP symptoms in a group of 15 hD patients.[105] However, research by *Pauli-Magnus* et al[104] found that naltrexone was ineffective as an antipruritic treatment for CKD-aP and was associated with a high incidence of side effects.[18]

Antihistamine Drugs and Mast-Cell Stabilizers

The positive effects of antihistamines in relieving itching were thought to be due to their sedative properties and their ability to stabilize mast cell membranes.[106] Despite a solid theoretical basis for their use, studies on histamine receptor antagonists yielded poor results in treating CKD-aP.[28] Trial outcomes were disappointing, and the risk of serious side effects, such as over-sedation—particularly in elderly patients—makes these medications less suitable for CKD-aP treatment.[28,106–109] In contrast, mast cell stabilizers showed promising results.[96,110,111] In a 4-week randomized controlled trial (RCT) involving 60 hD patients, the use of 4% cromolyn sodium cream applied twice daily significantly reduced itch severity compared to a placebo.[112] Additionally, in a 2-month double-blind RCT with 40 hD patients, zinc sulfate significantly improved CKD-aP symptoms compared to a placebo.[113] However, these results were not proved in a subsequent RCT.[114] Montelukast, a leukotriene receptor antagonist commonly used to treat asthma, allergic rhinitis, atopic dermatitis, and idiopathic urticaria, showed positive outcomes in reducing CKD-aP in two randomized, placebo-controlled studies.[115,116] However, both studies had a limited number of participants, and the average age of the patients was under 65 years, whereas most hemodialysis patients are typically over 65.[11] In general, nowadays antihistamines and mast cell stabilizers are not recommended in CKD-aP.

Tacrolimus Cream

One of the most well-designed trials evaluating immunomodulators for CKD-aP was a RCT of tacrolimus cream, which ultimately yielded negative results.[28] Tacrolimus cream, a topical calcineurin inhibitor with anti-inflammatory effects and minimal systemic absorption,[117] had previously shown promise in two uncontrolled trials that reported reduced itching.[118,119] However, in a 4-week, double-blind RCT involving 22 hemodialysis patients, the results indicated that while 0.1% tacrolimus cream reduced itching severity by around 80%, it was not significantly more effective than a placebo.[117] The study was complicated by an unexpectedly high reduction in itching—about 80%—in the placebo group, making it difficult to demonstrate the cream's superiority.[117]

Antidepressive Drugs

Mirtazapine, a serotonergic antagonist with antihistamine properties, showed effectiveness in reducing pruritus severity in a clinical trial involving 77 patients who were initially treated with gabapentin and then switched to mirtazapine.[120] Although mirtazapine appears to be beneficial in treating pruritus caused by intrathecal morphine, such as in CKD-aP, more high-quality studies are required to validate its effectiveness.[121] Although, some small studies reported that CKD-aP intensity decreased significantly with sertraline use, larger RCT with longer follow-up periods are required to prove its beneficial effect.[64,122,123]

Ondansetron

Ondansetron is a competitive antagonist of the serotonin 5-HT3 receptor and is commonly used to prevent and treat nausea and vomiting related to chemotherapy, radiotherapy, and surgery.[124,125] Additionally, it is used off-label, with varying degrees of success, to treat pruritus associated with cholestasis and to prevent opioid-induced itching.[126–131] Although *Balaskas* et al reported promising results for its use in managing CKD-aP, subsequent studies largely failed to confirm its efficacy.[107,132–136]

Discussion

Side Effects of Difelikefalin: A Comprehensive Perspective

Difelikefalin clinical efficacy in reducing itch intensity and improving quality of life was well-documented, a thorough discussion of its side effect profile is essential to provide a balanced perspective.

Clinical trials, KALM-1 and KALM-2 reported that the most frequently observed adverse events associated with difelikefalin include: a mild-to-moderate diarrhea that typically resolved without intervention, dose dependent nausea and vomiting that was likely related to the drug's systemic effects and dizziness that reported in a minority of patients.[14] Difelikefalin's action on the central nervous system (CNS) is limited due to its inability to cross the blood–brain barrier.[14] However, peripheral κ-opioid receptor activation could still lead to certain neurological effects, such as sedation and somnolence.[14] Although uncommon, hypotension was reported, likely due to peripheral receptor activation affecting vascular tone.[14] Patients with pre-existing cardiovascular instability could require close monitoring.[14]

There was a slight increase in the risk of infectious complications, including catheter-related infections, in hemodialysis patients receiving difelikefalin.[14]

The long-term safety profile of difelikefalin is still under investigation.[14] Current data from clinical trials and post-marketing surveillance suggest no major safety concerns, but ongoing studies will help determine the potential risks associated with chronic use, particularly in patients with multiple comorbidities.[14]

Understanding the side effects of difelikefalin is crucial for tailoring its use to individual patient needs. Proactive management of adverse effects—such as adjusting dosage, providing symptomatic relief, or monitoring high-risk patients—can optimize outcomes while minimizing discomfort. Moreover, these considerations emphasize the importance of shared decision-making, where the potential benefits of pruritus relief are weighed against the likelihood and severity of adverse effects.

Future Perspectives

B-type natriuretic peptide (BNP), also known as natriuretic polypeptide B, functions as a neurotransmitter in the murine itch response to various triggers.[28,137] Research showed that blocking natriuretic peptide receptor 1 could reduce itching in animal models.[138] This finding is particularly significant for dialysis patients, who tend to have elevated BNP levels that are associated with increased itching.[137] Other potential receptors involved in itch responses include mas-related G-protein–coupled receptors, protease-activated receptors 2 and 4, and the histamine-4 receptor.[139] In CKD, the retention of uremic toxins and metabolic disturbances leads to a state of systemic inflammation, involving elevated levels of pro-inflammatory cytokines like interleukin-31 (IL-31) and C-reactive protein (CRP).[140] This chronic inflammatory state can cause nerve sensitization and dysfunction in the skin, contributing to the sensation of itch.[140] Additionally, the upregulation of immune cells, such as T cells, mast cells, and macrophages, further exacerbates this inflammatory environment, intensifying the itch sensation.[140] Targeting these inflammatory pathways is a focus of therapeutic research, including trials involving nemolizumab a monoclonal antibody against the IL-31 receptor A.[147] Nemolizumab blocks the IL-31 signaling pathway, which is thought to play a significant role in pruritus.[141] Recent clinical trials of nemolizumab in CKD-aP patients showed promising results, with reductions in itch severity and improvement in quality of life compared to placebo.[9,65,140,141] These trials highlighted nemolizumab's potential as a targeted therapy that addresses the underlying inflammatory mechanisms of CKD-aP.[9,65,140,141]

The development of oral formulations of difelikefalin could be an exciting advancement in the management of CKD-aP and other pruritic conditions.[142,143] Although current evidence for difelikefalin primarily originate from studies of its intravenous formulation in hemodialysis patients, preliminary research into the oral form is underway.[142,143] Early-phase clinical trials suggested that oral difelikefalin demonstrates promising efficacy and safety profiles, expanding its potential use beyond dialysis-dependent patients to include those with earlier stages of chronic kidney disease or other pruritic disorders.[142,143] This oral formulation could improve patient convenience, adherence, and accessibility.[142,143] Further large-scale, randomized controlled trials are needed to confirm these findings and to explore its use in diverse populations.[142,143]

Summary

Although mentioned studies and medications could not present all possible treatment options for patients with CKD-aP, the authors attempted to conclude certain guidelines. In accordance with Spanish recommendations, patients with CKD should be screened for associated pruritus with KDQoL-36 and WI-NRS.[44] The baseline of the CKD-aP management is continuous use of emollients, optimal dialysis and hyperparathyroidism and hyperphosphatemia management. Emollients should have high water content. Oil-in-water emulsion with 15% glycerol and 10% paraffin, baths in polidocanol and emollients containing gamma-linolenic acid and sericin could bring additional relief for patients with CKD-aP. In case, when emollients would be insufficient, for mild CKD-aP topical 1% pramoxine lotion could be recommended and UVB therapy could be additionally considered.[13] If topical treatment and narrow band UVB do not bring relief, difelikefalin 0.5 μg/kg is recommended as first-line treatment for patients with moderate-to-severe CKD-aP. If difelikefalin is not available, pregabalin 25–75mg per day or gabapentin up to 300 mg per dialysis session could be administered in moderate-to-severe CKD-aP. This management approach, suitable for dialyzed patients, is visualized in Figure 2. Although similar management of non-dialyzed CKD-aP patients could be recommended, the difelikefalin should not be administrated. It does not have registration for non-dialyzed CKD-aP patients, and gabapentinoids should be recommended as a first-line systemic treatment. These CKD-aP management recommendations were supported by recent metanalysis, results of RCT's and expert's opinions.[11,13,123] Although, in KALM-1 and KALM-2 trials, difelikefalin was compared only to placebo, some expert opinions suggest that it should be first-line treatment in refractory CKD-aP.[11,144] Although, its efficacy was clearly demonstrated, approximately 20% of patients did not report clinically meaningful reductions in itch intensity, 30% did not present clinically relevant improvements in QoL.[145] Development of the new drugs targeting other neurotransmitters of the itch pathway or microinflmamation could bring a relief to the difelikefalin resistant CKD-aP patients.

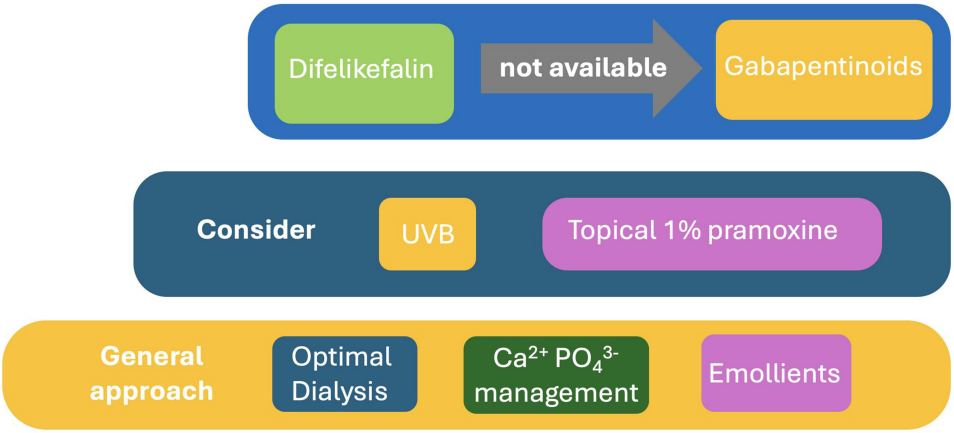

Figure 2 Proposal of stepwise management in dialyzed patients with chronic kidney disease associated pruritus (CKD-aP).

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