




CKJ REVIEW

Alleviating symptoms in patients undergoing long-term hemodialysis: a focus on chronic kidney disease-associated pruritus

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ABSTRACT

Since the breakthrough of kidney replacement therapy, increases in life expectancy for patients with end-stage kidney disease have been limited. However, patients have become increasingly vocal that, although mortality and life expectancy matter to them, the quality of their life, and particularly the relief of symptoms associated with their treatment, are in many cases more important. The majority of dialysis-associated symptoms and adverse effects do not currently have any approved treatments in this patient population, with the few treatments that are available used off-label, frequently without proven efficacy, yet still potentially adding further adverse effects to patients' current symptom burden. This article will illustrate how understanding the pathophysiology of a single, particularly burdensome symptom of dialysis (chronic kidney disease-associated pruritus) resulted in the design, development and regulatory approval of a treatment for that symptom. The pathway described here can be applied to other symptoms associated with dialysis, meaning that if we cannot add years to patients' lives, we can at least add life to their remaining years.

Keywords: chronic kidney disease-associated pruritus, dialysis, difelikefalin, quality of life, symptom relief

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Figure 1: Outline of the difelikefalin pathway, from symptom identification to regulatory approval.

INTRODUCTION

This article will illustrate the design, development and regulatory approval of a treatment for a single, particularly burdensome symptom of dialysis [chronic kidney disease-associated pruritus (CKD-aP)]. This was achieved through acknowledging the importance of CKD-aP symptom management to patients and understanding the symptom's underlying pathophysiology. This enabled the development of a treatment to target CKD-aP, utilizing clinical trials specifically designed to measure the impact and improvement of CKD-aP. Patient-reported outcomes (PROs) were used in all trials, enabling regulators to assess the value of this treatment in this patient population and therefore resulting in regulatory approval—a key point in the pathway to patient access (Fig. 1) [1].

SYMPTOM BURDEN AND ITS IMPORTANCE TO PATIENTS

Compared with the general population, the physical health-related quality of life (QoL) in patients with CKD [2] and in those with CKD on kidney replacement therapy [3] is substantially diminished; furthermore, the symptom burden is high [4, 5], with up to half of patients reporting at least one symptom as severe or overwhelming [6]. A growing recognition for the need to relieve symptoms in patients on dialysis offers an opportunity to address this in a scientifically robust way.

This lack of incorporation of patient priorities into treatment plans resulted in the development of the Standardized Outcomes in Nephrology (SONG) initiative [7], in which dialysis outcomes were aligned to the needs of all stakeholders (including patients, caregivers, clinicians, researchers and policy makers), with SONG-HD [8] and SONG-PD [9] focusing specifically on core outcomes relevant to hemodialysis (HD) and peritoneal dialysis (PD) stakeholders, respectively. Symptoms identified by SONG-HD as important include fatigue (a core outcome), depression, pain, anxiety, cramps, itching, nausea, restless legs syndrome, anemia, sexual function and sleep disturbance; the lack of food enjoyment, mobility, dialysis-free time or the ability to work or travel; as well as reduced cognitive function, the impact on family/friends, hospitalization and feeling washed out after diagnosis. Other initiatives, such as the Kidney Health Initiative [10], a public-private partnership between the American Society of Nephrology and US Food and Drug Administration, have also sought to develop a conceptual framework for symptom-based PROs, contributing to the development of PROs and electronic PROs (ePROs) to specifically assess HD treatment-related physical symptoms [11].

However, most dialysis-associated symptoms and adverse effects do not currently have any approved treatments in this patient population, resulting in a clear unmet need (Table 1). Health-related QoL in older or more frail patients has even been reported to be similar in patients who choose not to enter the dialysis pathway, due to the significant burden of symptoms

associated with dialysis [12]. The clear exception to the unmet need of treatments for dialysis adverse effects and symptoms is CKD-aP (and the associated impact on sleep disturbance), for which a specific treatment has recently been approved [13].

OVERVIEW OF CKD-aP (EPIDEMIOLOGY, ETIOLOGY, UNMET TREATMENT NEED)

CKD-aP is a prevalent and distressing condition for patients with kidney failure undergoing dialysis [14]. Recent data from the international observational Dialysis Outcomes and Practice Patterns Study (DOPPS) (phases 4–6; 2009–18) found that 67% of HD patients surveyed reported that they were bothered by pruritus, with 37% reporting moderate to extreme symptoms [15].

Pruritus as a symptom of HD has a unique underlying etiology compared with pruritus in the general population, meaning that common interventions for pruritus, such as moisturizers and topical corticosteroids [16], are often ineffective in the patients with kidney failure [17].

CKD-aP can significantly reduce the QoL of patients undergoing HD and can inhibit their ability to work or maintain an active social life [14, 17]. It is also associated with worse clinical outcomes, including an increased risk of infections and a higher rate of hospitalizations and mortality [15]. However, despite these negative aspects, CKD-aP still remains under-recognized by physicians [17].

CKD-aP frequently co-occurs with other physical and psycho-emotional symptoms experienced by HD patients, including poor sleep quality, depression, fatigue and pain [17–19], which together represent an important symptom cluster that is inadequately managed in clinical practice [20].

PATHOPHYSIOLOGY OF CKD-aP—THE CENTRAL ROLE OF THE OPIOID PATHWAY

Understanding the pathophysiology of CKD-aP was the essential first step before therapies could be developed. Although the pathophysiology is not yet fully understood, a combination of several mechanisms appears to contribute to its occurrence (Fig. 2). These include the accumulation of uremic toxins in the skin and activation of the non-histaminergic itch pathway [21], as a result of peripheral neuropathy, immune system dysregulation and/or opioid imbalance, with subsequent microinflammation and xerosis [22–24].

Elucidation of each of these mechanisms has provided a potential treatment pathway to alleviate CKD-aP; however, for many years, treatments with sufficient efficacy remained elusive. For example, toxin accumulation and deposition are now thought to cause CKD-aP in only a subset of patients, because increasing dialysis efficiency (with resulting decreasing Kt/V) and reducing serum calcium, parathyroid hormone or phosphorus all alleviate itching in only a small proportion of patients [23].

Peripheral neuropathy has been demonstrated to cause itching when diseased neurons are activated independently to the

Table 1: Overview of bothersome symptoms associated with dialysis and current treatment options.

Symptom	Treatment	Efficacy/safety	Approval/off-label for treatment of symptom?
Fatigue	Non-pharmacologic interventions: sleep hygiene, energy conservation, acupressure	Limited evidence of efficacy in small-scale studies [54]	NA
	Pharmacologic interventions: hematopoietics, antidepressants, anxiolytics, levocarnitine, human growth hormone, more frequent dialysis	Hematopoietics and antidepressants show some efficacy in patients with underlying anemia or depression Levocarnitine and human growth hormone have limited evidence of efficacy in small-scale studies Increased dialysis frequency has demonstrated efficacy but also increases overall time on dialysis [54]	Treatments approved for underlying conditions such as anemia and depression [54]
Depression	Psychotherapy	Some evidence of efficacy, although quality of evidence is low [55]	NA
	SSRIs	Limited evidence of efficacy in the dialysis population [55]	Approved in general population
Pain	Conservative management, e.g. exercise, massage, heat/cold therapy, cognitive behavioral therapy	Some evidence of efficacy, although quality of evidence is low [56]	NA
	Analgesics: opioid analgesics are indicated if pain control is not optimal with other methods Gabapentin/pregabalin	Evidence of efficacy in the general population, limited evidence in dialysis populations [56] Demonstrated efficacy in several small, short-term randomized trials conducted in patients on HD [57] Associated with increased risk of mental state changes and falls [57]	Approved in general population Recommended for the treatment of neuropathic pain in patients with kidney failure [58]
Anxiety	Psychotherapy	Some evidence of efficacy [59]	NA
	Pharmacologic agents, including SSRIs and benzodiazepines	Evidence of efficacy in the general population, limited evidence in dialysis populations Treatment with benzodiazepines is not suitable for long-term treatment [59]	Approved in general population
Cramps	Hypertonic solutions	Evidence of efficacy in patients on HD Mild post-dialysis hyperglycemia and hypernatremia have been reported [60]	NA
	Pharmacologic agents	Limited evidence of efficacy of quinine, vitamin E supplementation and L-carnitine [60, 61]	Off-label treatment
Restless legs syndrome	Non-pharmacologic: exercise, near-infrared light, vibration and massage	Limited evidence of efficacy in small-scale studies [62]	NA
	Pharmacologic: dopamine agonists, levodopa and iron supplements	Limited evidence of efficacy in small-scale studies [62]	Off-label treatment
	Parathyroidectomy	Limited evidence of efficacy in small-scale studies [62]	NA
Nausea	Ondansetron, metoclopramide and haloperidol	Evidence of efficacy for uremia-associated nausea [63]	Approved in general population

presence of pruritogens, with peripheral neuropathy highly prevalent in dialysis patients [23]. However, large-scale clinical trials of treatments that reduce pain associated with peripheral neuropathy have yet to show clear efficacy in CKD-aP, and although they have shown some efficacy in small-scale trials [25], they may also be associated with neurological adverse effects [26].

Immune system dysregulation still remains as a potential modulator of CKD-aP, as increased levels of eosinophils, mast cells, histamine and tryptase have all been reported; however, anti-histamines have limited efficacy against pruritus [23]. It is recognized that inflammation plays a key role in sensitizing the small nerve fibers in the skin that carry the itching sensation to the brain, producing the uncomfortable symptom of itching.

Table 1: Continued

Symptom	Treatment	Efficacy/safety	Approval/off-label for treatment of symptom?
Sleep disturbance	Non-pharmacologic: exercise and sleep hygiene	Evidence of efficacy in the general population, limited evidence in dialysis populations [64]	NA
Pruritus	Pharmacologic: treatment of underlying disorders, e.g. restless legs syndrome, pruritus or use of hypnotics	Evidence of efficacy in the general population, limited evidence in dialysis populations [64]	Several medications approved for insomnia in the general population—only eszopiclone is approved for longer-term use [64]
	Difelikefalin	Robust clinical efficacy and safety data from large well-designed Phase 3 RCTs [13, 46, 48]	Only treatment that is FDA-approved by regulatory authorities for treatment of CKD-aP
	Gabapentinoids (pregabalin and gabapentin)	Effective for reduction of itch intensity Risk of potentially serious adverse effects, particularly at higher doses, including altered mental status, falls and fractures [57]	Not approved for CKD-aP, off-label treatment

FDA, Food and Drug Administration; NA, not applicable; RCT, randomized controlled trial; SSRI, selective serotonin reuptake inhibitor.

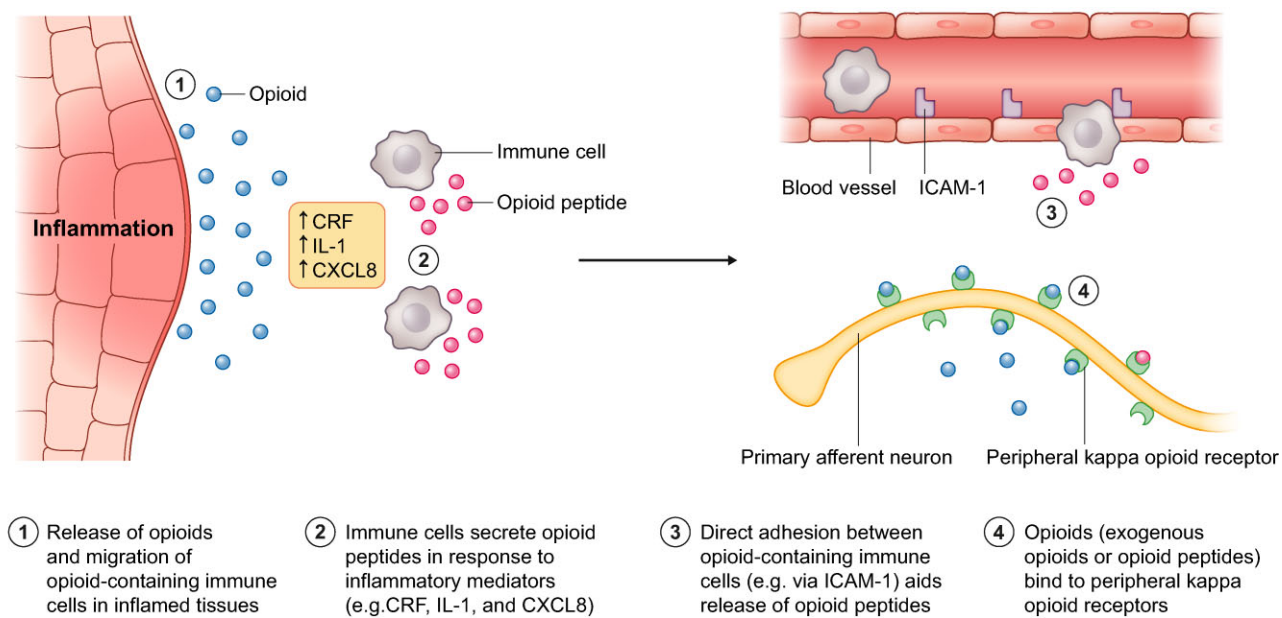


Figure 2: Pathophysiology of the itch mechanism through activation of kappa-opioid receptors in response to inflammation in CKD-aP. CRF, corticotropin-releasing factor; CXCL8, C-X-C motif chemokine ligand 8; ICAM-1, intercellular adhesion molecule 1; IL-1, interleukin-1.

Furthermore, high levels of markers of systemic inflammation are observed in patients with CKD-aP, including high levels of T cells and white blood cells, C-reactive protein, interleukins-6 and -2, and ferritin, alongside low levels of albumin [27].

ROLE OF OPIOID RECEPTORS IN THE PATHOGENESIS OF ITCHING

Imbalance in the endogenous opioid system, characterized by overexpression of mu-opioid receptors (MOR) signaling and downregulation of kappa-opioid receptor (KOR) signaling, has been implicated in the pathogenesis of itch in CKD-aP [28]. Fur-

thermore, MOR and KOR expression imbalance has been observed in the skin of patients with CKD-aP in comparison with those free from itch [29]. Several drugs that act on the MOR and/or KOR have been evaluated for the treatment of CKD-aP, such as naltrexone, loratadine and nalbuphine; however, in clinical trials these have mostly reported limited efficacy [30–34]. There are some promising studies with the partial MOR agonist and KOR agonist, nalfurafine hydrochloride, which at higher doses demonstrated significant reductions in itch intensity, as measured through the Worst Itch Numeric Rating Scale (WINTRS) [34] and visual analogue scale [33]. Nalfurafine is currently approved for the treatment of CKD-aP in Japan and South Korea.

The MOR and KOR pathways therefore remain a promising target for the systemic relief of CKD-aP, resulting in the development of difelikefalin.

THE DEVELOPMENT OF DIFELIKEFALIN

Difelikefalin is a selective, peripherally restricted KOR agonist recently approved in the USA and Europe for the treatment of moderate-to-severe pruritus in patients undergoing HD [13, 35]. Difelikefalin was developed as an analogue of an endogenous opioid peptide, Dynorphin A, which is known to be a neuromodulator of pruritus [36]. Similar to Dynorphin A and other KOR agonists, difelikefalin is thought to alleviate itch by activating KORs on peripheral sensory neurons and immune cells [36, 37]. In order to limit the potential for psychotomimetic and dysphoric effects observed with some other KOR agonists, the chemical structure of difelikefalin was chosen to ensure it was not a substrate for drug uptake transporters, and would not be significantly metabolized. The half-life of difelikefalin is 23–31 h in patients undergoing HD; plasma concentrations of difelikefalin were reduced by 70%–80% following HD, with difelikefalin undetectable in plasma following two dialysis cycles [38].

THE ASSESSMENT OF CKD-aP

Nephrologists are familiar with measurements of multiple variables tracked over time so they can accurately quantify disease progression. For example, we have measurements of kidney injury through urine albumin to urine creatinine ratio and measurement of kidney failure through measurement of estimated glomerular filtration rate, and together they are used to stage kidney disease. Such a staging system allows for the appropriate use of diagnostic procedures and the institution of treatments, and provides a prognosis of future progression of kidney disease and cardiovascular events in such patients. Conversely, symptoms have not been subjected to this scrutiny.

Because there is no test for a symptom chain, such as serum creatinine or a urine test, a tool is necessary to monitor the symptom over time. The clinical impact of CKD-aP can be quantified in two domains by the severity of the symptom and the impact of the symptom on the patient's wellbeing. The assessment of symptoms in a bidimensional framework—severity and impact—lends itself well to the examination of the response to therapy. Although many PROs have been tried to gauge the severity of CKD-aP, few have been rigorously tested, and using such a tool was the primary mechanism for regulatory approval.

For patients diagnosed with CKD-aP, the assessment of pruritus severity should therefore incorporate an evaluation of both the level of itch intensity and the impact of itch on patient QoL (Fig. 3).

QUANTIFYING ITCH INTENSITY AND THE EFFECT OF ITCHING ON A PATIENT'S QOL

Several validated unidimensional and multidimensional PRO scales are available for the assessment of itch intensity and itch-related QoL in patients with CKD-aP [39].

For example, The Self-Assessed Disease Severity (SADS) questionnaire is validated for assessing the impact of itch severity [40, 41]. This is a simple and appropriate tool that enables patients rapidly to self-assess the similarity of three descriptions to symptoms experienced by the patients. Thus, the SADS questionnaire allows patients to classify themselves into one of

three “types” of patient (A, B or C), depending on the presence of scratch marks on the skin, the impact of itching on sleep and the presence of agitation/sadness due to itching, ranging from type A (mild) to type C (severe). Although this tool has not been used in the difelikefalin clinical studies to date, its use is proposed in the treatment algorithm; in clinical trials we can obtain relatively high completion rates for more complex, multi-question QoL tools which may also take substantial time and resources to analyze, whereas the use of single-question (unidimensional) scales are the easiest and most time-efficient measures for assessing patient-reported itch intensity in clinical practice. The use of the 24-h WI-NRS has also been developed as a useful, single-question tool to assess rapidly the severity of itch. The WI-NRS consists of a validated 11-point scale ranging from 0 (“no itch”) to 10 (“worst itch imaginable”), and patients rate the intensity of their worst itching during the previous 24-h period [40, 42, 43], with a 3-point improvement on the scale validated as a meaningful improvement [39].

Based on the WI-NRS score and SADS category, pruritus can be categorized as “mild” or “moderate-to-severe” (WI-NRS score ≥ 4 ; SADS patient type B or C). This could be useful to plot pruritus trajectories in individual patients.

Other appropriate validated unidimensional scales for measurement of itch intensity that may be used include the visual analogue scale (100-mm line) and verbal rating scale (4-point scale) [40, 42].

The impact of itch on the patient's QoL can also be evaluated by asking the patient about how itch affects their sleep or mood, through the use of a validated PRO measure.

Several available validated dermatological PRO questionnaires can be used to assess the impact of itch on QoL (Table 2), including the Skindex-10 [40], 5-D itch [44] and Dermatology Life Quality Index [45]. These instruments are frequently utilized in clinical research but may not be as convenient to use in clinical practice due to their length, complexity and time required to complete and evaluate the responses.

Questionnaires may not be suitable for some patients (e.g. individuals with severe visual/cognitive impairment); instead, these patients can be asked verbally about how itch impacts their QoL. However, it is important to recognize that questionnaires may not be a viable method to assess disease severity and QoL in all patients; language barriers or literacy barriers, as well as lack of patient interest in completing surveys, can all impact the use of PROs, although this may be improved with the use of ePROs [11].

Among therapies to treat symptoms in patients on HD, to our knowledge, difelikefalin has the largest clinical development program of any kappa agonist for CKD-aP in HD, with 1306 patients receiving active treatment in Phase 3 trials, of whom 400 received at least 1 year of continuous treatment [13, 46, 47].

However, it was the early phases of the drug development program that formed the basis for the later success of the clinical trials. Of particular importance for difelikefalin was the demonstration of its lack of mu-agonist activity or metabolism and minimal peripheral restriction, with a subsequent abuse assessment study confirming that it has low potential as a drug of abuse [38] and is therefore not considered a controlled substance [13].

The efficacy and safety of intravenous difelikefalin were evaluated by two pivotal randomized, placebo-controlled, Phase 3 trials (KALM-1 and KALM-2) [13, 47, 48], which enrolled a total of 851 adult patients on HD with moderate-to-severe pruritus. In each of the two trials, patients received intravenous difelikefalin 0.5 $\mu\text{g/kg}$ of dry body weight or placebo after HD

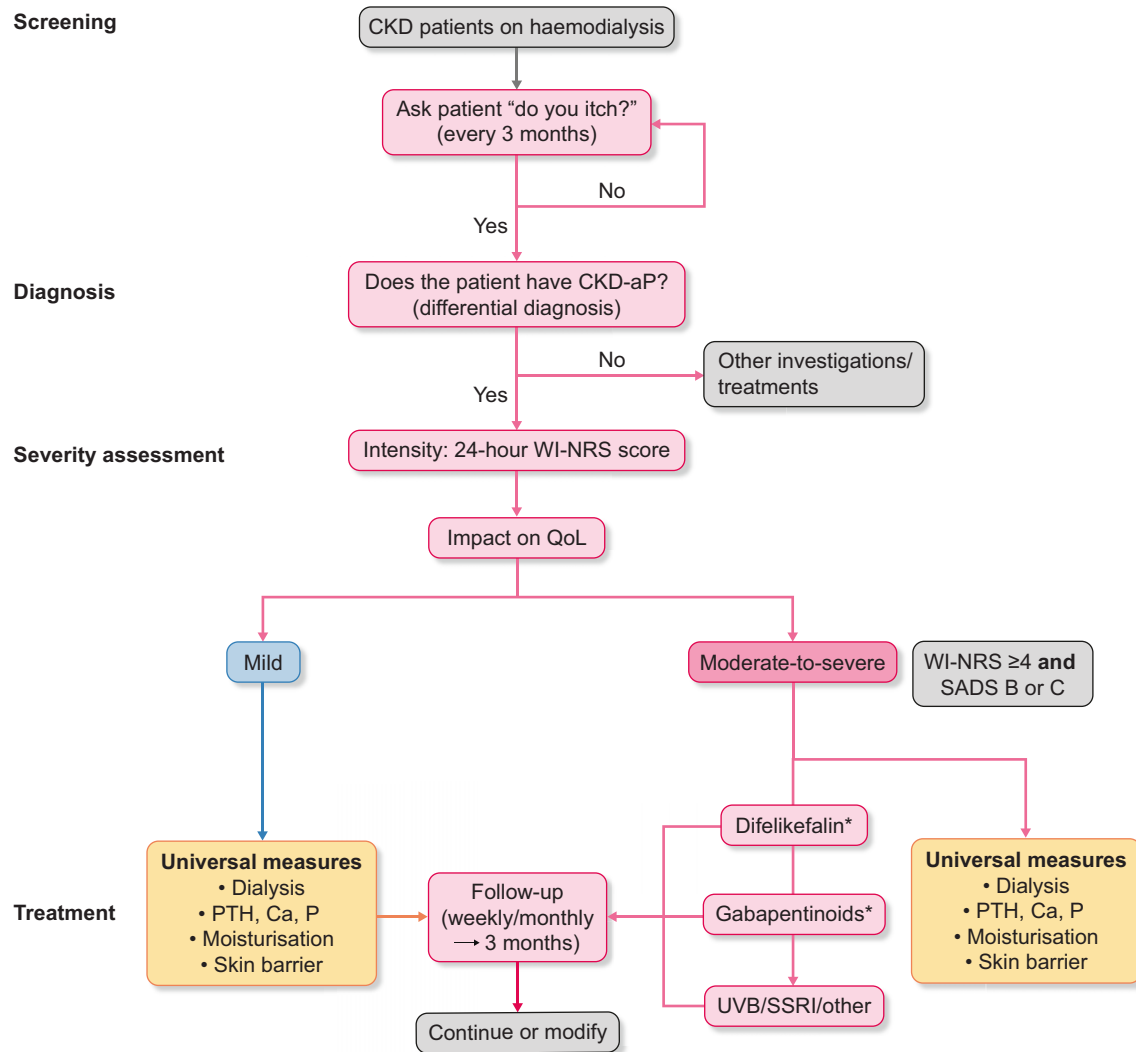


Figure 3: Proposed algorithm for the screening, diagnosis, assessment and treatment of CKD-aP among patients undergoing HD. *Treatment selection dependent on the availability of difelikefalin. Ca, calcium; NRS, numerical rating scale; P, phosphorus; PTH, parathyroid hormone; SSRI, selective serotonin reuptake inhibitor; UVB, ultraviolet B; VRS, verbal rating scale.

sessions three times per week for 12 weeks. As well as clinical measures of efficacy, these trials utilized validated PRO measures of disease severity and itch-related QoL, enabling direct measurement of the improvement of CKD-aP symptom burden in this specific patient population. The proportion of patients achieving a ≥ 3 -point greater decrease from baseline in daily 24-h WI-NRS scores was significantly greater with difelikefalin versus placebo at week 12 (KALM-1: 49% versus 28%, $P < .001$; KALM-2: 54% versus 42%, $P = .02$), as well as at each week throughout the study, with significant improvements in itch-related QoL also reported at Week 12 for Skindex-10 and 5-D itch PROs (Fig. 4) [46, 47]. Pooled safety analysis of KALM-1 and KALM-2 showed that frequent adverse events occurring at an incidence of $\geq 2\%$ with difelikefalin and $\geq 1\%$ higher than in the placebo group included: diarrhea (9.0% versus 5.7% with placebo), dizziness (6.8% versus 3.8%), nausea (6.6% versus 4.5%), gait disturbances, including falls (6.6% versus 5.4%) and hyperkalemia (4.7% versus 3.5%) [49].

Additionally, in conjunction with improving itch severity, treatment with difelikefalin has been shown to significantly improve sleep quality compared with placebo (evaluated through the Sleep Quality Questionnaire and 5-D itch scale sleep disability question), both of which are key burdensome symptoms for patients [8, 50–52].

In the KALM studies, patients continued any existing anti-itch medications. Although around one-third of patients were prescribed concomitant anti-itch medications, the majority were using antihistamines, which are unlikely to be effective in CKD-aP, because CKD-aP is not thought to involve a histaminergic pathway [21]. Only 1.2% of patients were prescribed gabapentoids as an anti-itch medication (although some patients were also prescribed gabapentoids for non-itch-related conditions). The treatment algorithm for CKD-aP (Fig. 3) therefore proposes initiating treatment with difelikefalin, as the only approved therapy for this condition in the US and Europe as well as the only treatment with several large-scale clinical

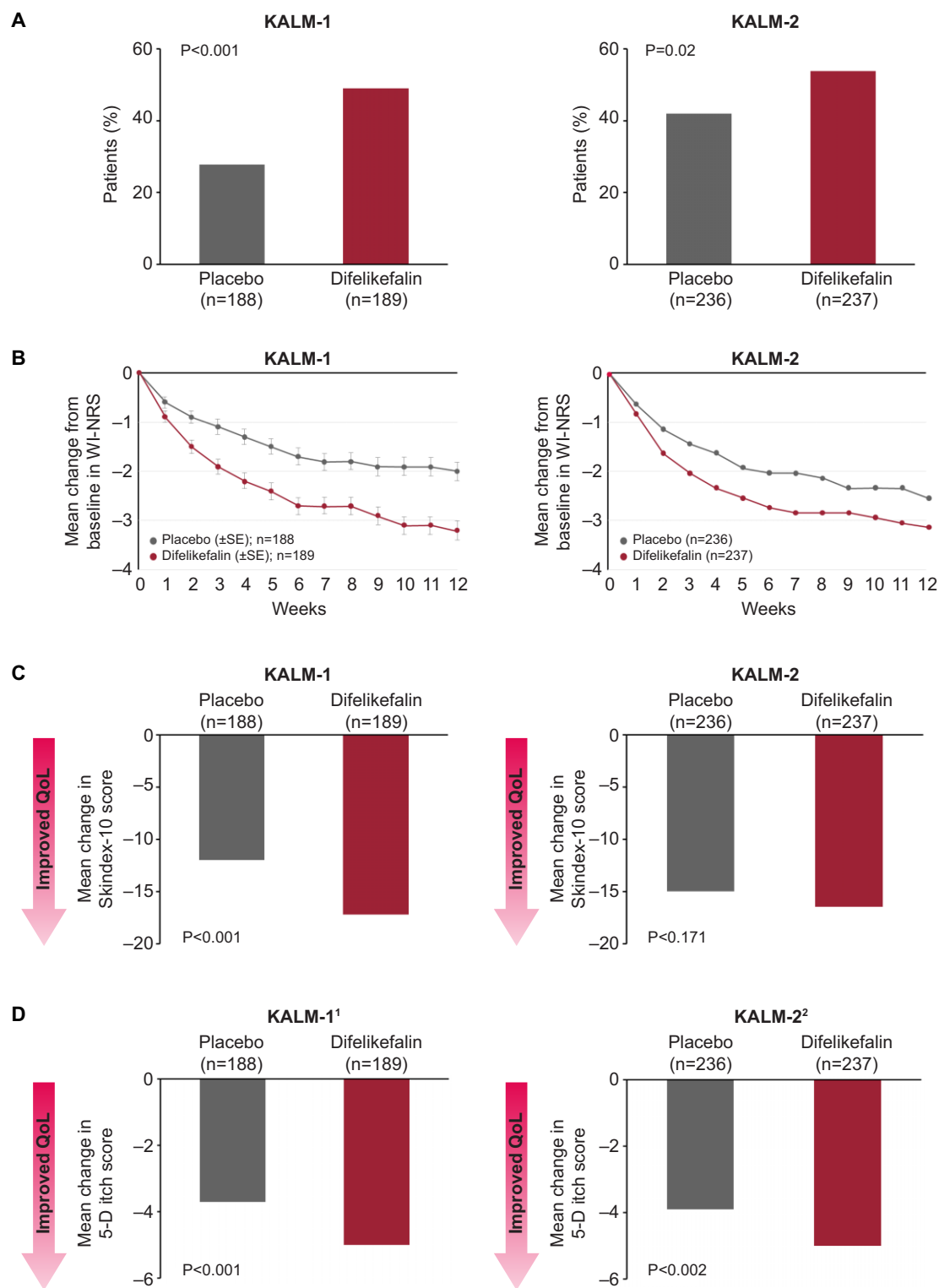


Figure 4: Improvement in itch severity and itch-related QoL with difelikefalin versus placebo, measured by (a) ≤ 3 -point improvement in WI-NRS, (b) weekly improvement in WI-NRS, (c) Skindex-10 and (d) 5-D itch scale. SE, standard error. References: Fishbane et al. *N Engl J Med* 2020;382:222–32; Wooldridge et al. *J Am Soc Nephrol* 2020;31:22–23.

Table 2: Overview of itch-related PRO measures.

Measure	Description
WI-NRS	11-point scale of itch intensity over the previous 24-h period (range 0 to 10; higher scores indicate greater itch intensity), which has been validated in patients with CKD-aP [40, 42, 43]. Reduction of ≥ 3 points on the WI-NRS has been shown to be associated with a clinically meaningful change in itch intensity for patients with moderate-to-severe pruritus undergoing HD [43].
SADS	SADS categorizes patients into one of three self-designated types (A, B or C), depending on the presence of scratch marks on the skin, the impact of itching on sleep, and the presence of agitation/sadness due to itching [40, 41].
Skindex-10	Multidimensional tool to evaluate the impact on itch-related QoL of CKD-aP across three separate itch-related domains: Disease, Mood/Emotional Distress and Social Functioning [65]. Skindex-10 total scores range from 0 to 60, with worsening itch-related QoL indicated by higher scores. Analysis of Phase 2 clinical trial data in adult HD patients with moderate-to-severe pruritus indicated that a ≥ 15 -point reduction (improvement) from baseline in the total Skindex-10 score represents a clinically meaningful change [52].
5-D itch	Multidimensional tool that assesses itch-related QoL and itch intensity across five separate itch-related domains (Duration, Degree, Direction, Disability and Distribution) over a 2-week recall period [44]. 5-D itch scale total scores range from 5 to 25, with worsening itch intensity and itch-related QoL indicated by higher scores. Analysis of Phase 2 clinical trial data indicates that a clinically meaningful improvement was represented by a reduction from baseline of ≥ 5 -point in the total 5-D itch score [52].
Sleep Quality Numerical Rating Scale	11-point scale to indicate how much itch interfered with sleep over the preceding 24 h, with responses ranging from 0 ("did not interfere") to 10 ("completely interfered").
Patient self-categorization of pruritus severity	Patients select which of three patient profiles they are most like according to occurrence of scratch marks on skin, problems sleeping because of itching and feelings of agitations or sadness: Patient A (mild signs and symptoms), Patient B (moderate signs and symptoms) or Patient C (severe signs and symptoms).
MOS sleep scale	6-point scale ranging from "all of the time (0)" to "none of the time (6)" to indicate the frequency of various aspects of sleep disruption. Also records estimates of average hours of sleep during the past week and length of time taken to fall asleep. Higher scores reflect better sleep-related HRQoL.
PGI-S	Single-item scale with five possible values ranging from none to very severe to assess patient impression of itch severity; higher scores reflect worse severity.
PGI-C	Single-item measure with values ranging from "1" (Very Much Improved) to "7" (Very Much Worse); higher scores reflect worse status to assess patient impression of change (improvement or worsening) in overall status relative to the start of the study.
M-PGIC	Single-item measure with four response options: "My itch got worse," "No change," "My itch got better but the amount of improvement was not meaningful to me" and "My itch got better and the amount of improvement was meaningful to me" to assess patients' overall impression of change in itch during the course of the clinical trial and whether the amount of improvement was meaningful to them.
Dermatology Life Quality Index	10 questions concerning patients' perception of the impact of skin diseases on different aspects of their HRQoL over the last week, calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired [45].

HRQoL, health-related quality of life; MOS, Medical Outcomes Study; PGI-S, Patient Global Impression of Worst Itch Severity; PGI-C, Patient Global Impression of Change; M-PGIC, modified Patient Global Impression of Change.

trials in this patient population. However, the safety data from the clinical studies has demonstrated that patients may continue concomitant anti-itch medications already prescribed, if desired.

If patients are contraindicated for difelikefalin, it is not available, or resistant disease is reported, the use of gabapentoids is suggested as alternative or additional treatment, followed by other therapies such as phototherapy or selective serotonin reuptake inhibitors, which have some evidence of efficacy in small, uncontrolled clinical trials [53].

SUMMARY

Patients with CKD undergoing kidney replacement therapy report many particularly burdensome symptoms. Treatments for these symptoms, where available at all, are frequently used off-label, with limited evidence of efficacy and safety in the CKD population.

The development of difelikefalin to treat CKD-aP demonstrates a pathway from symptom identification and understanding of the underlying pathophysiology, through drug development and demonstration of efficacy and safety, to regulatory approval and patient access, and therefore, ultimately, symptom relief and associated improvements in QoL.

However, there are many symptoms of dialysis with an unacceptable unmet need remaining; it is hoped that the example of difelikefalin can be followed to successfully treat or relieve other symptoms and side effects of dialysis—in the absence of adding years to patients' lives, we can at least add life into their remaining years.

NEXT STEPS

The example of CKD-aP illustrates that treatment of symptoms using a double-blind controlled trial is possible. Such treatments can now be applied to other unmet need areas, such as

cramping, depression, fatigue and pain, among patients with CKD to alleviate symptoms and improve QoL.

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DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

R.A. reports personal fees and nonfinancial support from Bayer Healthcare Pharmaceuticals Inc., during the conduct of the study; he also reports personal fees and nonfinancial support from Akebia Therapeutics, Relypsa, Vifor Pharma, Boehringer Ingelheim and Eli Lilly; he has received personal fees from Lexicon, Reata and Diamed; he is a member of data safety monitoring committees for Chinook and Vertex; he is a member of steering committees of randomized trials for Akebia Therapeutics and Bayer; he is a member of adjudication committees for AbbVie, Bayer, Boehringer Ingelheim and Janssen; he has served as associate editor of the *American Journal of Nephrology* and *Nephrology Dialysis Transplantation*, and has been an author for UpToDate; and he has received research grants from the US Veterans Administration and the National Institutes of Health. J.B. reports fees from Vifor Pharma. M.G. reports fees from Vifor Pharma. K.K.-Z. reports fees from Vifor Pharma, Kabi and AstraZeneca. G.M. reports speaker or advisory board honoraria from AbbVie, Astellas, Boehringer Ingelheim, Novo Nordisk and Sanofi. C.P. has no conflicts to disclose. J.C.S. has no conflicts to disclose.

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