

A Systematic Review of Efficacy and Safety of Difelikefalin in Treating Pruritus in Hemodialysis Patients with Chronic Kidney Disease

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Abstract

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Background: Chronic Kidney Disease (CKD) is a type of kidney disease that gradual loss of kidney function over a period of months or years, usually more than 3 months. Uremic pruritus or chronic kidney disease-associated with CKD (CKD-aP) is a common complication that experienced by CKD patients especially for patients undergoing haemodialysis and it will negatively impact quality of life, for example depression, poor sleep quality, and miss dialysis sessions.

Methods: Three online databases were used for the literature search: Science Direct, Embase, and PubMed. obtaining the information in January 2024. Using specific keywords, a comprehensive analysis of research articles was carried out. We examined the safety and effectiveness of difelikefalin in the management of pruritus in patients receiving hemodialysis who have chronic kidney disease.

Result: Six studies were evaluated that met the criteria for inclusion. The efficacy of difelikefalin in all studies was examined by using WI-NRS as assessment tools for the primary outcome, and for the secondary outcome, skindex-10 or skindex-16 scoring, the 5-D itch scale, and the itch MOS (Medical Outcome Study) sleep disturbance scale were used. From all studies, difelikefalin in various dosages and routes (oral and intravenous) improved pruritus reduction in hemodialysis patients with CKD over placebo. However, in the majority of cases, difelikefalin caused a higher chance of experiencing adverse events than in the placebo group.

Conclusions: All studies show a greater pruritus reduction in hemodialysis patients receiving therapy over placebo, with the optimal benefit-risk at 0.5 µg/kg of difelikefalin, despite unclear efficacy-dosage connections.

Introduction

Chronic Kidney Disease (CKD) is a type of kidney disease that causes gradual loss of kidney function over a period of months or years, usually more than 3

months. Uremic pruritus or chronic kidney disease-associated with CKD (CKD-aP) is a common complication that is experienced by CKD patients especially for patients undergoing haemodialysis. Pruritus linked to CKD may be caused by abnormalities in endogenous opioid receptor activation.¹

Targeting peripheral kappa opioids receptors (KOR), difelikefalin is the first medication to be specifically licensed for the treatment of moderate-severe CKD-aP in patients receiving hemodialysis in the USA and Europe. Up to 40% of hemodialysis patients reported being moderate-extremely bothered by itching in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Difelikefalin may also enhance sleep and quality of life when it comes to itching. Pruritus related to CKD will negatively impact quality of life, for example depression, poor sleep quality, and miss dialysis sessions.²

For hemodialysis patients with chronic kidney disease, the medication's safety and efficacy were critical considerations. This study will assess numerous factors that can reduce pruritic symptoms in hemodialysis patients with chronic kidney disease (CKD), including dosage, routes, side events, etc. Many methods are available to analyze the results, such the skindex-10 or skindex-16 scoring, the 5-D itch scale, the itch MOS (Medical Outcome Study) the sleep disturbance scale, and the WI-NRS (Worst Itch Numeric Rating Scale).

The effectiveness and safety of difelikefalin from multiple clinical trials will be presented in this study. The investigation of the function of activated kappa opioid receptors in the regulation of CKD-related systemic itch during hemodialysis is another goal of this work. Apart from that, there are still a few studies that have reviewed this matter systematically to enhance evidence-based medicine.³

Material and Methods

Data Sources and Search Strategy

For this systematic review, three online databases were searched in January 2024: PubMed, Embase, and Science Direct. The search turned up 99 papers (21 from PubMed, 22 from Embase, and 56 from Science Direct) when the terms pruritus patient on hemodialysis were combined with AND

efficacy OR effectiveness and AND difelikefalin. When we limited our search to pruritus patient on hemodialysis, published in the past 10 years randomized clinical trials, human studies, English publications, and the efficacy and/or effectiveness and safety of difelikefalin, we discovered 21 studies (3 from PubMed, 13 from Embase, and 4 from Science Direct). Three reviewers (ME, YK, and GHT) read the entire text. We eliminated from this research any studies that are not publicly available, in the form of presentations or posters, and have been published more than once. Consequently, there are six studies in the final selection stage (3 from PubMed and 3 from Embase) to form this systematic review.

Quality Assessment

We followed the PRISMA statement (<http://www.prisma-statement.org>) when conducting this systematic review. The Cochrane Collaboration risk of bias assessment (<http://methods.cochrane.org/bias/assessing-risk-bias-included-studies>) was then used to methodically evaluate the trial quality. Following the collection of studies, a more thorough evaluation of each study's eligibility was carried out, as shown in Figure 1.

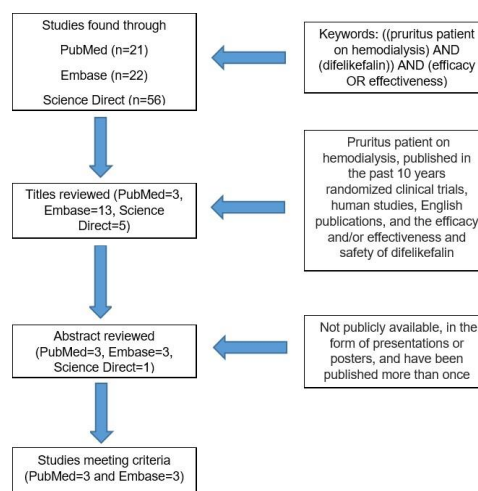


Figure 1. Flowchart of Study Collection

Table 1. Characteristics of Studies

| Study & Location | Design | N | Study Criteria | Medications | Primary Outcome (Efficacy) | Secondary Outcome (Efficacy) | Adverse Event (Safety) |
|---------------------------------|--|---|---|--|---|---|---|
| Fishbane et al.4 (2019) - US | Phase 3 double-blind, placebo controlled RCT with open label extension | 189 and 188 subjects in difelikefalin and placebo group respectively | Inclusion criteria: age \geq 18 years (mean=58.2 \pm 11.2 difelikefalin group, 56.8 \pm 13.9 in placebo group), with end-stage kidney disease, had been undergoing hemodialysis at least 3 times per week for at least 3 months, had moderate-to-severe pruritus. | 0.5 μ g/kg difelikefalin or matched placebo intravenously three times a week for 12 weeks | \geq 3-Point improvement from baseline at week 12 in the weekly mean scores of the daily 24-hr WI-NRS scores: difelikefalin group > placebo group (49.1% vs 27.9%; RR, 1.65. 95% CI, 1.26-2.14; P<0.001) | Least-square mean change from baseline at week 12 in 5-D itch scale total scores: difelikefalin group > placebo group (-5.0 \pm 0.3 vs -3.7 \pm 0.3, P<0.001) | 12-week double-blind intervention period: placebo group 62.2% = difelikefalin group 62.2% (overall AE) |
| | | | | | \geq 4-Point improvement from baseline at week 12 in the weekly mean scores of the daily 2-hr WI-NRS: difelikefalin group > placebo group (37.1 (28.3-46.9) vs 17.9 (12.1-25.8), RR, 1.92. 95% CI, 1.37-2.68; P<0.001) | Least-square mean change from baseline at week 12 in Skindex-10 scale total scores: difelikefalin group > placebo group (-17.2 \pm 1.3 vs -12.0 \pm 1.2, P<0.001) | 2-week discontinuation period: placebo group 24.6% > difelikefalin group 19.9% (overall AE) |
| Yosipovitch et al.5 (2023) - US | Phase 2 double-blind, placebo-controlled RCT | 69, 66, 67, 67 subjects in 0.25 mg, 0.5 mg, 1 mg, placebo difelikefalin groups respectively | Inclusion criteria: age \geq 18 years (mean=65.7, 69, 67.5, 65.6, from difelikefalin 0.25 mg, 0.5 mg, 1 mg, and placebo group respectively), had moderate-severe renal impairment, had been receiving hemodialysis 3 times a week for \geq 3 months, had moderate-to-severe pruritus. | 0.25 mg, 0.5 mg, 1 mg, placebo difelikefalin orally once daily for 12 weeks (divided to 3 treatment groups and 1 placebo group) | \geq 3- and \geq 4-Point improvement of WI-NRS at week 12: 14.4% < 31.6% (P-value:0.037) < 33% (P-value=0.027) < 38.6 (P=0.006) (placebo < 0.5 mg < 0.25 mg < 1 mg difelikefalin groups, respectively) | Least-square mean change from baseline at week 12 in 5-D itch total scores: -5.7 < -6.2 (P value=0.515) < -6.8 (P value: 0.099) < -7.0 (P=0.070) in placebo, 0.25 mg, 0.5 mg, and 1 mg difelikefalin groups respectively. Least-square mean change from baseline at week 12 in Skindex-10 total scores: -20.0 < -21.2 (P-value=0.580) < -22.1 (P-value:0.335) < -23.6 (P=0.116) in placebo, 0.25 mg, 0.5 mg, and 1 mg difelikefalin groups respectively | 50.7% < 51.5% < 58.2% in placebo and 0.25 mg, 0.5 mg, and 1 mg difelikefalin groups respectively (overall AE) HD subjects > NDD-CKD subjects (TEAEs) |
| Narita et al.6 (2022) - Japan | Phase 2 double-blind, placebo-controlled RCT, multicenter, 4-arm, parallel-group | 59, 53, 54, 59 subjects in 0.25 μ g/kg, 0.5 μ g/kg, 1 μ g/kg, placebo difelikefalin groups respectively | Inclusion criteria: age \geq 20 years (mean=64.5, SD=11.7), had ESKD and moderate-severe pruritus, had been receiving maintenance hemodialysis 3 times a week for at least 12 weeks, were nonresponse to systemic treatment (e.c.: antihistamines, and/or antiallergic drugs) and/or topical antipruritic moisturizers and a moderate or severe baseline Shiratori severity scores for 2 days or more in the 7 days preceding the start of treatment. | 0.25 μ g/kg, 0.5 μ g/kg, 1 μ g/kg, placebo difelikefalin intravenously at the end of each hemodialysis session 3 times a week for 8 weeks (divided to 3 treatments groups and 1 placebo group) | \geq 3-Point improvement of WI-NRS at week 8: 50% < 53% < 57% < 60% (placebo < 0.25 μ g/kg < 1 μ g/kg < 0.5 μ g/kg difelikefalin groups, respectively) | Adjusted weekly mean skindex-16 overall scores at week 8: -22.69. (SE=2.04) < -24.04 (SE=1.94) in placebo group < -24.25 (SE=1.96) < -27.79 (SE=2.05) in 1 μ g/kg, placebo, 0.25 μ g/kg, and 0.5 μ g/kg difelikefalin groups respectively | 67% < 72% < 77% < 85% in placebo 0.25 μ g/kg, 0.5 μ g/kg, 1 μ g/kg difelikefalin groups, respectively (overall AE) |
| | | | | | Exclusion criteria: the pruritus was not associated with CKD, had liver cirrhosis as complication, history of phorotherapy, history of adverse events attributable to nalfurafine, and history of drug hypersensitivity to opioids. | \geq 4-Point improvement of WI-NRS at week 8: 34% < 36% < 43% < 51% (0.25 μ g/kg < placebo < 1 μ g/kg, < 0.5 μ g/kg difelikefalin groups, respectively) | Adjusted weekly mean 5-D itch scale total scores at week 8: -5.8 (SE=0.3) < -6.6 (SE=0.3) < -6.5 (SE=0.4) < -6.8 (SE=0.3) in placebo, 0.25 μ g/kg, 0.5 μ g/kg, and 1 μ g/kg difelikefalin groups respectively |

| | | | | | | | |
|---|--|--|---|---|---|--|---|
| Fishbane et al.7 (2020) - US | Phase 2 double-blind, placebo-controlled RCT | 44, 41, 44, 45 subjects in 0.5 µg/kg, 1 µg/kg, 1.5 µg/kg, placebo difelikefalin groups respectively | Inclusion criteria: male or female adults, ≥ 18 years, had ESRD, had been receiving hemodialysis three times a week for at least three months prior to screening, had experienced persistent pruritus in the month preceding screening, with a weekly mean WI-NRS scores over the 7 days preceding randomization greater than 4 (ranging from 0 [no itching] to 10 [worst imaginable]). | 0.5 µg/kg, 1 µg/kg, 1.5 µg/kg, placebo difelikefalin intravenously at the end of each hemodialysis session 3 times a week for 8 weeks (divided to 3 treatment groups and 1 placebo group) | <p>≥ 3-Point improvement of WI-NRS at week 8: 29% < 59% < 64% < 67% (placebo < all combined < 0.5 µg/kg < 1.5 µg/kg difelikefalin groups, respectively)</p> <p>≥ 4-Point improvement of WI-NRS at week 8: 24% < 44% < 51% (placebo < all combined < 0.5 µg/kg difelikefalin groups, respectively)</p> | <p>Least-square mean change from baseline at week 8 in Skindex-10 total scores: -8.2 (SEM=2.0) < -18.7 (SEM=2.0) < -15.5 (SEM=2.2) < -15.1 (SEM=2.3), 16.4 (SEM=1.3) in placebo, 0.5 µg/kg, 1 µg/kg, and 1.5 µg/kg, all combined difelikefalin groups respectively</p> <p>Least-square mean change from baseline at week 8 in 5-D itch total scores: -2.8 (SEM=0.5) < -4.7 (SEM=0.6) < -5.3 (SEM=0.3) < -5.4 (SEM=0.6) < -5.7 (SEM=0.5) in placebo, 1.5 µg/kg, all combined, 1 µg/kg, 0.5 µg/kg difelikefalin groups respectively</p> <p>Least-square mean change from baseline at week 8 in itch MOS sleep disturbance scores: -1.3 (SEM=3.1) < -6.9 (SEM=3.5) < -11.8 (SEM=2.0) < -13.8 (SEM=3.2) < -14.6 (SEM=3.4) in placebo, 1.5 µg/kg, all combined, 0.5 µg/kg, 1 µg/kg difelikefalin groups respectively</p> | 42.2% < 70.7% < 77.3% < 77.5% < 84.1% in placebo, 1.0 µg/kg, 1.5 µg/kg, all combined, 0.5 µg/kg difelikefalin groups, respectively (overall AE) |
| Topf et al.8 (2022) - North America, Europe, and the Asia-Pacific region | Phase-3 double-blind, placebo controlled RCT with open label extension | 426 and 425 subjects in difelikefalin and placebo groups respectively (these subjects were randomized in the pooled KALM-1 and KALM 2 studies) | Inclusion criteria: ≥ 18 years (mean=58.3 and 59.1 in placebo and difelikefalin groups, respectively), had been treated by HD 3 times perweek for ≥ 3 months before screening. Exclusion criteria: had a scheduled kidney transplant during the study, had a concomitant disease or history of any medical condition, had been using new anti-itch treatments within 14 days before screening. | 0.5 mcg/kg or placebo difelikefalin intravenously for 12 weeks | <p>≥ 3-Point reduction in the weekly mean of daily WI-NRS at week 12 in KALM-1: 28.3% < 50.9% (placebo < difelikefalin groups, respectively)</p> <p>≥ 3-Point reduction in the weekly mean of daily WI-NRS at week 12 in KALM-2: 42.6% < 53.4% (placebo < difelikefalin groups, respectively)</p> <p>≥ 4-Point reduction in the weekly mean of daily WI-NRS at week 12 in KALM-1: 18% < 38.4% (placebo < difelikefalin groups, respectively)</p> <p>≥ 4-Point reduction in the weekly mean of daily WI-NRS at week 12 in KALM-2: 26.4% < 37.3% (placebo < difelikefalin groups, respectively)</p> | <p>≥ 15-Point improvements in Skindex-10 total scores at week 12: 40.5% < 55% (placebo vs difelikefalin groups, respectively)</p> <p>≥ 15-Point improvements in 5-D itch total scores at week 12: 42.3% < 52.1% (placebo vs difelikefalin groups, respectively)</p> <p>Least-square mean change from baseline at week 12 in Skindex-10 scores: -13.5 < -6.9 (placebo vs difelikefalin groups, respectively)</p> <p>Least-square mean change from baseline at week 12 in 5-D itch total scores: -3.7 < -4.9 (placebo vs difelikefalin groups, respectively)</p> | Overall AE: 3.8% < 6.3% (placebo vs difelikefalin groups, respectively) |

| | | | | | | | |
|---|--|--|--|---|---|---|---|
| Fishbane et al.9 (2022) - North America, Europe, and the Asia-Pacific region | Phase-3 double blind, placebo-controlled povotal phase 3, open-label studies | 424, 424 subjects in difelikefalin and placebo, respectively | Inclusion criteria: ≥ 18 years (mean=58.4, 59, 58.3 in placebo, difelikefalin, and all-difelikefalin exposure cohort), had ESRD and were treated by HD 3 times per week for ≥ 3 months, had moderate-to-severe CKD-aP at baseline. | 0.5 mcg/kg or placebo difelikefalin 3 times per week at the end of each dialysis session for 12 weeks | - | - | TEAE: 65.3% < 71.2% (placebo vs difelikefalin) |
| | | | Exclusion criteria: the use of new antipruritic medications after screening. | | | | AEs leading to death: 1.2% > 0.7% (placebo vs difelikefalin groups, respectively) |

Result

Literature Search

Seven citations' titles and abstracts from papers published in the previous ten years were examined. Because one of the studies used a clinical trial without a placebo, we had to eliminate it from our evaluation. Six studies in all fulfilled the search criteria, which included reporting the efficacy and safety of difelikefalin in treating pruritus related to chronic kidney disease in patients who had been receiving hemodialysis. Table 1 includes study design, number of patients, study criteria, medications, primary and secondary outcome.

Study Characteristics

The titles and abstracts of seven publications published during the last 10 years were analyzed. One study had to be excluded from our analysis as it employed a clinical trial without a control group. The search parameters were satisfied by six papers total, including those that reported on the safety and effectiveness of difelikefalin in treating pruritus associated with chronic kidney disease in hemodialysis patients. The primary and secondary outcomes, study criteria, number of patients, drugs, and trial design are all listed in Table 1. Numerous criteria were shared by all six studies. For example, those older than eighteen years, had end-stage renal disease or chronic kidney disease, for which hemodialysis was the treatment of choice three times a week for at least three months before the screening. The six studies were

randomized controlled trials (RCTs) with a placebo. The major outcomes were assessed using the WI-NRS (Worst Itch Numeric Rating Scale) scores, while the secondary outcomes were assessed using the 5-D itch scale, itch MOS (Medical Outcome Study) sleep disturbance, skindex-10, or skindex-16 scoring.

Administration of Difelikefalin

Difelikefalin and its placebo were given intravenously in five out of the six studies; as a result, only one research (Yosipovitch et al., 2023) delivered difelikefalin orally.⁵ Oral difelikefalin was given once a day for 12 weeks by Yosipovitch et al. In the other studies, intravenous difelikefalin was administered three times a week, for eight to twelve weeks, following hemodialysis sessions.

Efficacy and Safety of Difelikefalin

Difelikefalin is a medication used to treat chronic renal disease-related pruritus. Difelikefalin (orally or intravenously) reduces pruritus in patients with chronic kidney disease. After two or three months of administering difelikefalin, ≥3- and/or 4-point improvements in WI-NRS as primary outcome showed that all of the trials demonstrated that difelikefalin produces superior results than a placebo group. The secondary outcome for those studies were evaluated using the 5-D itch scale, itch MOS sleep disturbance, skindex-10, or skindex-16, at two or three months after starting difelikefalin administration from baseline to examine the efficacy as well. All scores decreased more in difelikefalin groups

rather than in placebo groups, whether it was orally or intravenously administered. Some studies conducted the trial by giving one group the same dose, and some divided difelikefalin administration into several groups with different doses for each group (Fishbane et al., 2019; Yosipovitch et al., 2023; Narita et al., 2022).⁴⁻⁶

The safety of difelikefalin was evaluated based on AEs. According to Yosipovitch et al. (2023)⁵, hemodialysis patients had a higher likelihood of treatment-emergent adverse events (TEAEs) or adverse events that started after the commencement of the trial drug compared to non-dialysis-dependent chronic kidney disease (NDD-CKD).

Dizziness and gastrointestinal AEs, which are the most prevalent TEAEs, were noted due to comorbidities and more severe illness in HD individuals. The majority of the studies showed overall AEs or TEAEs were found to be more common in difelikefalin groups than in placebo groups. However, Fishbane et al. (2022) showed AEs leading to death were found more in the placebo group than in the difelikefalin group (1.2% vs. 0.7%).⁹

Discussion

In order to determine the effectiveness and safety of difelikefalin in treating pruritus-related renal disease in hemodialysis patients, this article thoroughly reviewed the six most pertinent intervention trials. According to this review, the difelikefalin group showed a higher reduction in pruritus than the placebo group, as measured by the WI-NRS score, which was used to examine the primary outcome. For the secondary outcome, skindex-10 or skindex-16 scoring, the 5-D itch scale, the itch MOS (Medical Outcome Study), and the sleep disturbance scale were used in certain studies.

Three research conducted by Yosipovitch et al., Narita et al., Fishbane et al. (2020), compared the efficacy of difelikefalin starting from 0.25 µg/kg to 1.5

µg/kg. According to those three studies, the correlation between effectiveness and dosage has not reached a fixed answer.

Fishbane et al. (2020) and Narita et al. examined the efficacy based on WI-NRS scores after 8 weeks. However, from a study conducted by Fishbane et al., the highest ≥ 3 -Point improvement of WI-NRS score after 8 weeks was found in the 0.5 µg/kg difelikefalin group. Meanwhile Narita et al., revealed the 1.5 µg/kg group gave the highest ≥ 3 -Point improvement of WI-NRS score.

The lowest dose of difelikefalin that was given in all six research was 0.25 µg/kg. At the lowest dose, the difelikefalin group was still greater in giving improvement than placebo. The reason for this event is associated with the rate of drug clearance in hemodialysis patients. Hence, at all dosages, the exposure levels and difelikefalin efficacy were reached.⁴⁻⁶

Difelikefalin is a selective agonist of kappa opioid receptors that is selectively limited to the peripheral nervous system. It is thought to have a significant role in controlling chronic kidney disease associated with pruritus. Nevertheless, during the 12-week difelikefalin trial, there was no indication of abuse or any signs of physical dependence.⁹ With one exception of a study by Fishbane et al. (2019), where the incidence in both trial groups was high and indicative of the vulnerable group of patients who present with serious other medical conditions, difelikefalin groups generally caused more adverse events than placebo groups.

Regarding safety, the majority of research revealed that AEs increased in frequency in a way that was dose dependent. Across all trials, nausea, vomiting, dizziness, diarrhea, and disturbances in gait were the most frequently reported adverse events. A dosage of 0.5 µg/kg of difelikefalin proved to have the most favorable benefit-risk profile. Difelikefalin's reaction at 0.25 µg/kg was clearly insufficient, as demonstrated by dose-response analysis, and it was safe to use up to 1.0 µg/kg.⁶

Conclusion

Many methods of evaluation showed that the group receiving therapy reduced pruritus more than the placebo group in hemodialysis patients with chronic renal disease, while the efficacy

and dosage connection remain unresolved. Defelikefalin's safety varies according to dose. Consequently, it was discovered that 0.5 µg/kg of difelikefalin provided the optimal benefit-risk profile.

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