Survey Report

Perception mapping of Indian Physicians on Difelikefalin for the treatment of moderate to-severe itching (pruritus) associated with chronic kidney disease (CKD-aP) in adults undergoing hemodialysis (HD)

Version No.: 1.0

The study was conducted according to the approved protocol and in compliance with the protocol, Good Clinical Practice (GCP), and other applicable local regulatory requirements.

Contents

1. INTRODUCTION

Pruritus is an unpleasant comorbidity that frequently affects individuals with end-stage renal disease (ESRD), chronic kidney disease (CKD), and dialysis. It reduces these individuals' quality of life (QOL). The pruritus associated with CKD has been named "uremic pruritus." However, because there is no direct association between pruritus and uremia, the term "CKD-associated pruritus" (CKD-aP) is recommended [1]. The prevalence of CKD-aP has varied significantly between studies. It has been observed to range between 20% and as high as 90% [2-4]. Xerosis causes dry, scaly skin. It has been observed to be a prominent feature among pruritus patients [5]. Patients with CKD-aP showed elevated amounts of mast cells in their dermis [6]. A study by ozen, et al. found WBC counts ≥ 6.7 × 103/μL increased the risk of pruritus by 1.73 times. Serum proinflammatory cytokines (IL-6, CRP, etc.) were found to be higher in CKD-aP patients [7].

The treatment for CKD-aP includes management of xerosis, use of antihistamine, uremic toxin removal and opioid mediators such as difelikefalin. Difelikefalin, a new opioid agonist with significant kappa-opioid receptor (KOR) selectivity, has been demonstrated to be useful in the treatment of persistent pruritus and post-operative pain [8]. KOR activation on peripheral sensory neurons limits afferent transmission of sensory signals to the central nervous system. Furthermore, this medication possesses immunomodulatory properties. It has been demonstrated to activate KORs on immune system cells, resulting in reduced production of pro-inflammatory cytokines and inflammation [9, 10]. Importantly, due to its hydrophilic qualities, transit across the blood-brain barrier is limited. Compared to many other opioids, such as fentanyl or morphine, difelikefalin has less effect on the central nervous system and does not cause respiratory depression or sedation [8]. The Food and medicine Administration (FDA) approved difelikefalin in August 2021, and the European Medicines Agency (EMA) approved it in April 2022 as the first medicine to treat CKD-aP in adult hemodialysis patients. The suggested dose is 0.5 μg per kg body weight. The medicine is given as an intravenous injection at the end of the hemodialysis session [11]. In a randomized clinical trial, Viscusi et al. found that difelikefalin delivered intravenously at doses of 1.0 and 5.0 μg/kg did not produce respiratory depression. The side effects, such as somnolence or paresthesia, were minimal and did not require intervention. Because of its lack of action on mu-opioid receptor

(MOR), no euphoric effect was noticed when using difelikefalin; thus, the addictive potential of this chemical is negligible [12].

Overall, difelikefalin is a useful drug for specific conditions like CKD-aP specifically patients on HD. The use of this drug has no euphoric effects and safe in patients. Continuous monitoring and further studies are necessary to better understand its safety and efficacy across these drugs.

2. RATIONALE OF THE STUDY

The rationale for exploring Indian physicians' perceptions of difelikefalin in treating moderate-to-severe pruritus associated with CKD-aP in adults undergoing HD was rooted in the significant burden and quality-of-life impairment caused by CKD-aP. As this condition affected up to 70% of end-stage kidney disease patients, with many experiencing severe itching, the availability of effective treatments like difelikefalin—a selective kappa-opioid receptor agonist approved for this purpose—presented a new therapeutic opportunity. Understanding physicians' awareness, acceptance, and prescribing patterns of difelikefalin was crucial, particularly in India, where patient outcomes were closely tied to both clinical practice and physician attitudes. These insights aimed to guide education efforts, optimize treatment strategies, and address any barriers to the adoption of this promising therapy.

The survey was designed to explore and map physicians' perceptions of difelikefalin and its therapeutic indication. The rationale for conducting the survey included the management of conditions like CKD-aP, the emergence of difelikefalin as a novel therapy, the need to understand its acceptance and use in combination treatments, and the alignment of clinical guidelines with real-world practice. By assessing physician perspectives, the survey sought to identify the factors influencing the adoption of difelikefalin and its combinations, as well as any barriers that hindered its wider application in clinical practice. This provided valuable insights into optimizing CKD-aP management and improving patient outcomes.

3. OBJECTIVES

The primary objective of this study was to assess the perception, practice patterns, and clinical experiences of Indian physicians regarding the therapy indication and the use of difelikefalin associated with CKD-aP in HD.

4. METHODS

This study was a cross-sectional, questionnaire-based survey designed to assess Indian physicians' perceptions, practices, and clinical experiences regarding the use of difelikefalin in managing CKD-aP. The study involved a structured 15-question survey distributed electronically to licensed physicians across various regions of India, particularly those practicing nephrology, dermatology, or related fields. The questionnaire gathered data on the frequency of difelikefalin use, treatment protocols, perceptions of efficacy and safety, and factors influencing its indication. The study aimed to provide insights into the real-world application of difelikefalin and inform future guidelines and best practices.

Physicians were selected through professional networks and medical associations, and participation required informed consent. Exclusion criteria included individuals without relevant clinical experience, such as medical students or administrative staff. Data were collected securely and analyzed using descriptive and inferential statistics, such as chi-square tests or logistic regression, to identify trends and relationships between physician characteristics and prescribing behaviors. Ethical approval was obtained, ensuring participant confidentiality and the right to withdraw at any time.

The study design was well-suited to capture a snapshot of current practices, without the need for randomization or blinding, as the goal was to collect subjective data on physician experiences rather than assess treatment efficacy. With a target sample size of 100 physicians, the study provided a comprehensive overview of difelikefalin's role in clinical practice in India, identifying patterns that could inform future research or clinical guidelines.

5. RESULTS

A total of 81 HCPs participated in the survey. Below is the summary of the responses.

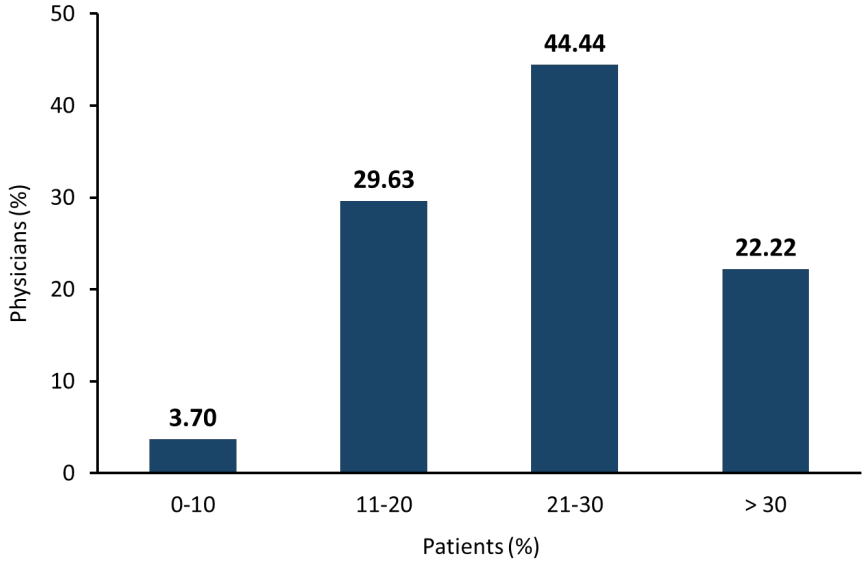
[1] In your clinical practice, what is the prevalence of Pruritus in haemodialysis patients?

a. 0-10%

b. 11-20%

c. 21-30%

d. >30%



- Approximately 44.44% of physicians observed a prevalence of pruritus in 21–30% of hemodialysis patients in their clinical practice.
- About 29.63% of physicians indicated that pruritus affects 11–20% of hemodialysis patients in their clinical practice.
- A significant portion of physicians (22.22%) noted that pruritus affects more than 30% of hemodialysis patients in their clinical practice.
- A small group of physicians (3.70%) reported that pruritus affects 0–10% of hemodialysis patients in their clinical practice.

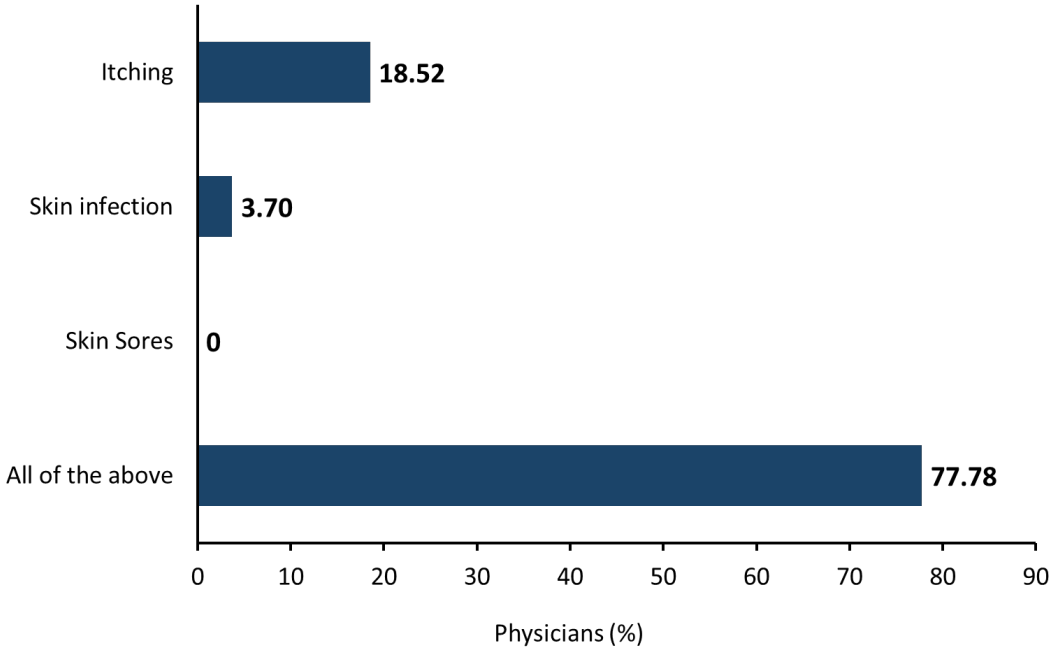
[2] What are the most common sign & symptoms you observed in patients with CKD –associated pruritus?

a. Itching

b. Skin Sores

c. Skin Infection

d. All of the above

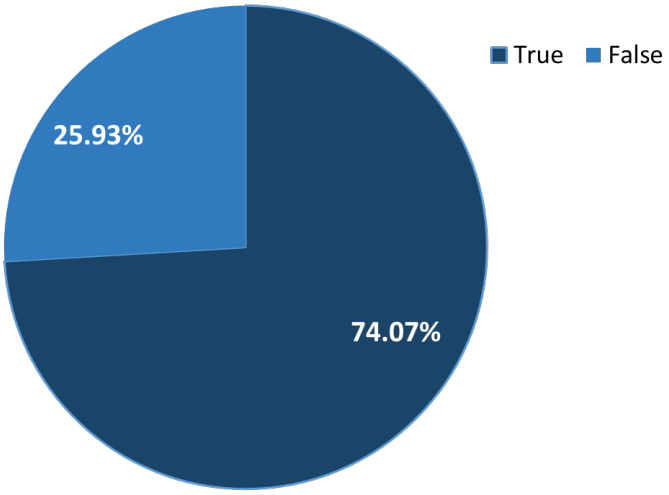


- Itching, skin sores, and skin infections—were the most common sign & symptoms observed by 77.78% of physicians in patients with CKD – associated pruritus.
- Itching was identified as a common symptom of CKD-associated pruritus by 18.52% of physicians.
- No physician reported skin sores as a symptom in patients with CKD-associated pruritus.
- Skin infections were reported as a symptom of CKD-associated pruritus by 3.70% of physicians.

[3] CKD –associated pruritus can happen without any signs on the skin?

a. True

b. False

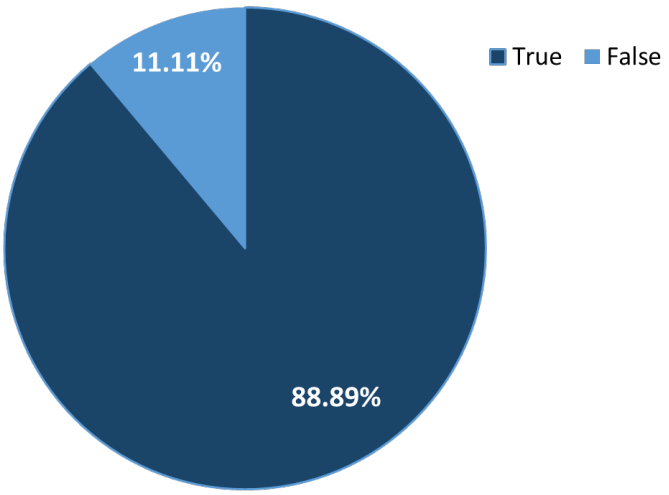


- The majority of physicians (74.07%) confirm that pruritus in CKD patients can occur even in the absence of skin abnormalities.
- A smaller proportion of physicians (25.93%) disagree, indicating that they believe skin signs are always present with CKD-associated pruritus.

[4] CKD –associated pruritus can happen along with xerosis?

a. True

b. False



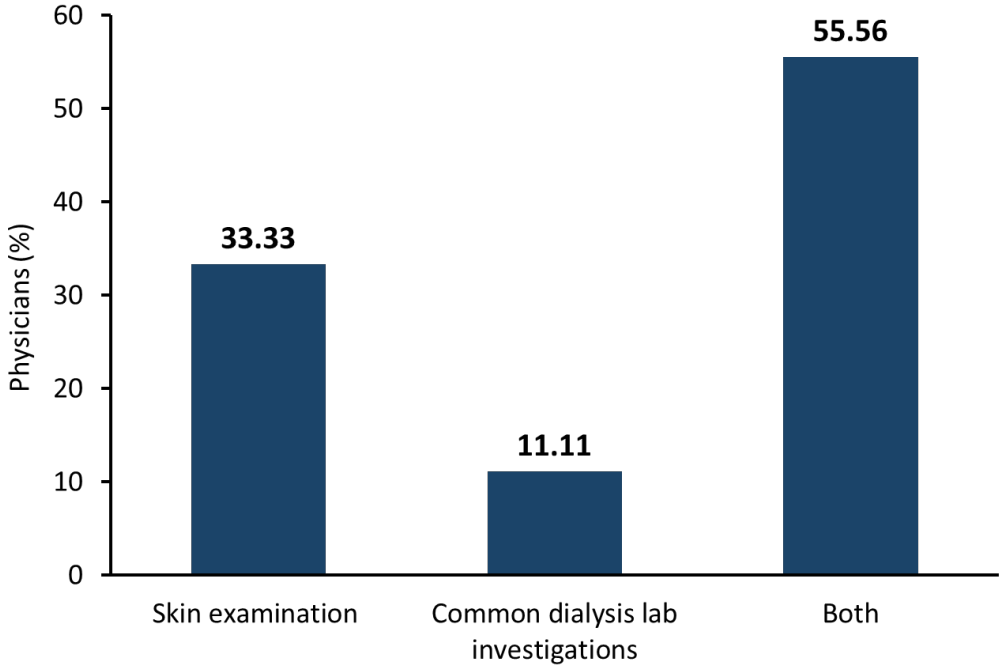
- The majority of physicians, 88.89%, believe that xerosis is commonly associated with CKD-related pruritus.
- A smaller proportion, 11.11%, do not consider xerosis as a factor in CKD-associated pruritus.

[5] How do you diagnose patients with CKD –associated pruritus?

a. Skin Examination

b. Common dialysis Lab Investigations

c. Both a & b



- The majority of physicians (55.56%) prefer a combined approach of skin examination and lab investigations for diagnosing CKD-associated pruritus.
- About 33.33% of physicians diagnose CKD-associated pruritus through skin examination.
- Approximately 11.11% of physicians rely on common dialysis lab investigations to diagnose CKD-associated pruritus.

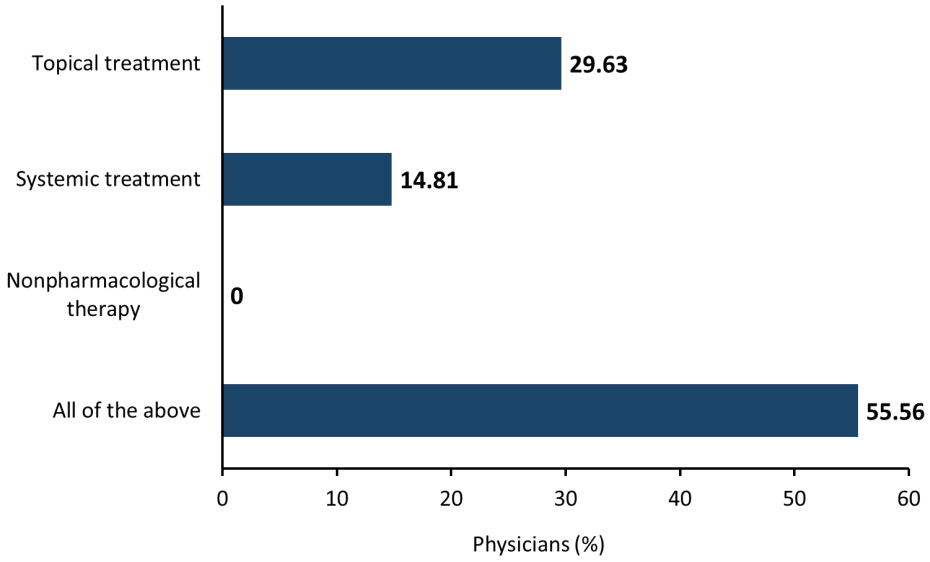
[6] How do you treat patients with CKD –associated pruritus?

a. Nonpharmacological therapy (Phototherapy, Accupuncture)

b. Topical treatment (Emollients, Topical analgesics, Topical Tacrolimus, Topical Steroids)

c. Systemic Treatment (Antihistamines, Gabapentinoids, Opioids)

d. All of the above



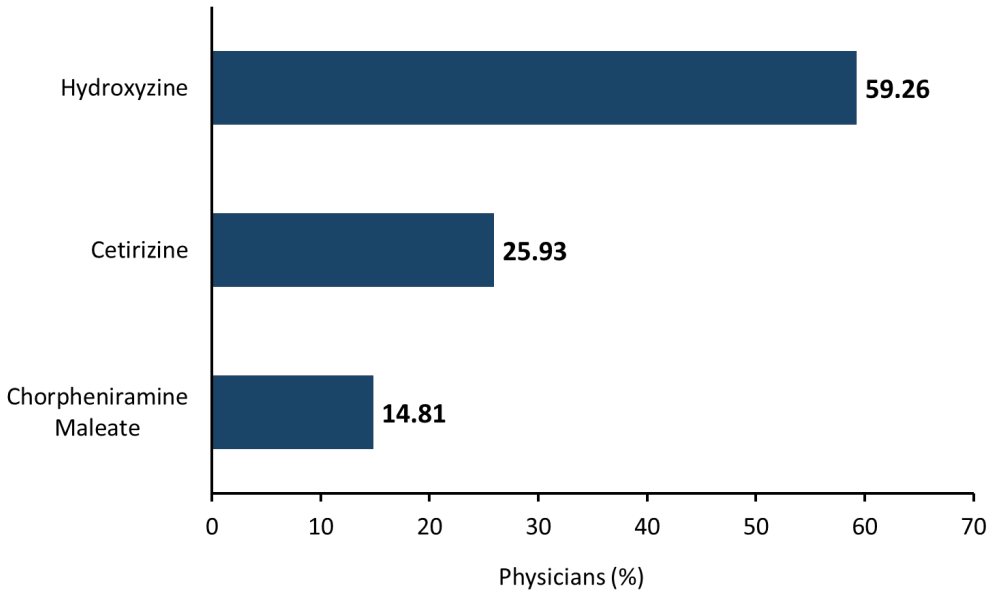
- A majority (55.56%) of physicians preferred a combined approach using all available treatments, suggesting that a multimodal strategy is often favored for managing CKD-associated pruritus.
- Topical treatments, including emollients, topical analgesics, tacrolimus, and steroids, were chosen by 29.63% of physicians, indicating their moderate popularity.
- Systemic treatments, such as antihistamines, gabapentinoids, and opioids, were selected by 14.81% of physicians, reflecting a less frequent approach.
- Nonpharmacological therapies, such as phototherapy and acupuncture, are not commonly used for CKD-associated pruritus, with no physicians selecting this option.

[7] Which antihistamine drug do you prefer for treatment of HD CKD pruritus patients?

a. Hydroxyzine

b. Cetirizine

c. Chorpheniramine Maleate



- Hydroxyzine was the most preferred antihistamine for treating pruritus in HD CKD patients, with 59.26% of physicians selecting it.
- Cetirizine was chosen by 25.93% of physicians, making it the second most commonly preferred option.
- Chlorpheniramine maleate was the least preferred, with only 14.81% of physicians opting for it.

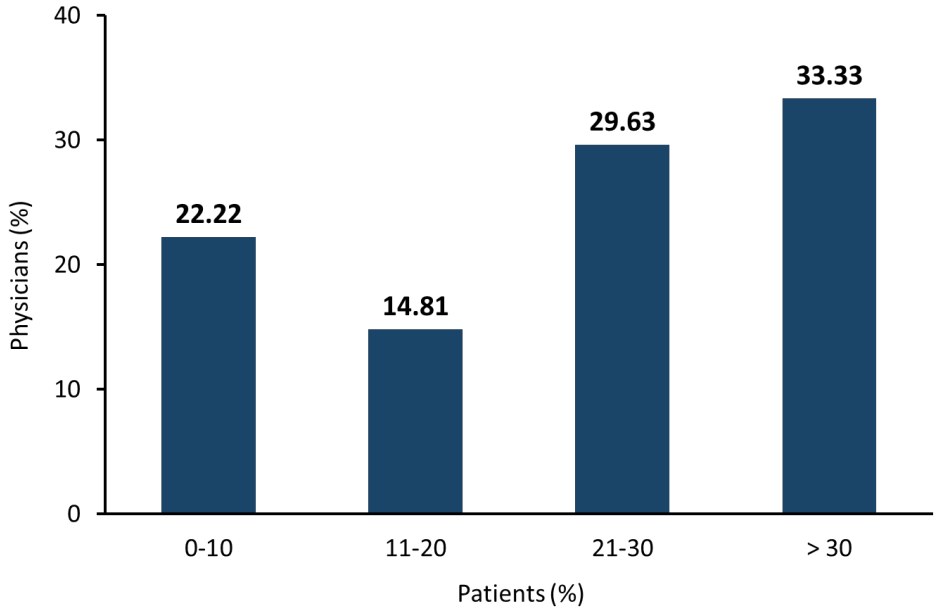
[8] How many percentages of HD CKD pruritus patients does not respond to overall available treatment?

a. 0-10%

b. 11-20%

c. 21-30%

d. >30%



- According to 22.22% of physicians, 0-10% of HD CKD pruritus patients do not respond to available treatments.
- A smaller group, 14.81% of physicians, reported that 11-20% of patients show resistance to treatment.
- The largest proportion, 29.63% of physicians, estimated that 21-30% of patients fail to respond to current therapies.
- Notably, 33.33% of physicians indicated that more than 30% of patients do not achieve relief, highlighting a significant challenge in managing pruritus in this population.

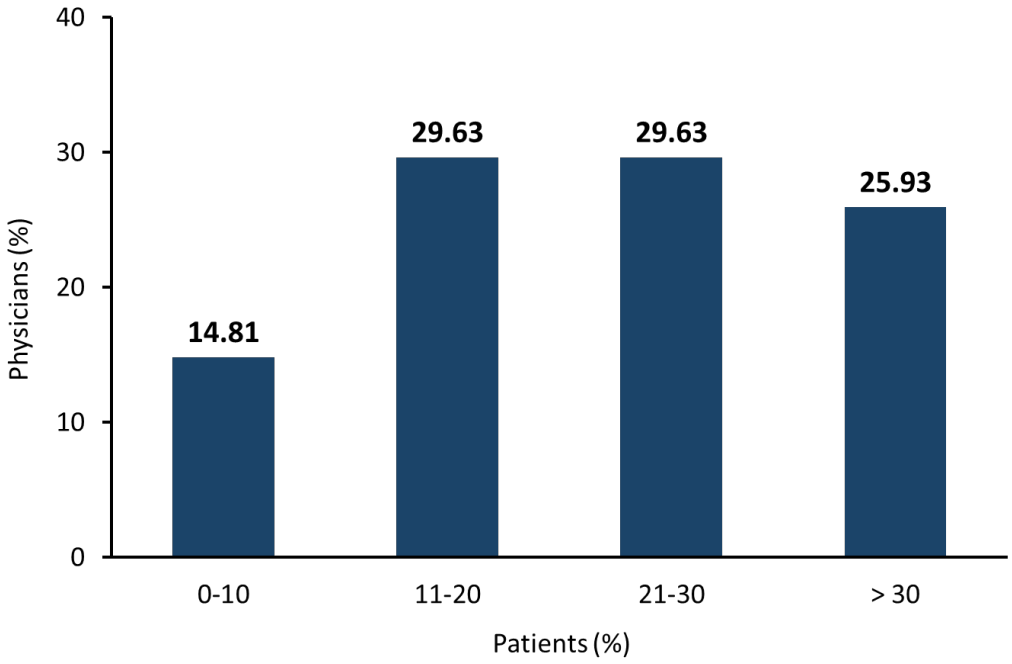
[9] How many percentages of HD CKD pruritus patients does not respond to topical treatment?

a. 0-10%

b. 11-20%

c. 21-30%

d. >30%



- A small proportion of physicians (14.81%) reported that only 0-10% of HD CKD pruritus patients do not respond to topical treatment.
- Both 11-20% and 21-30% non-responsiveness rates were reported by 29.63% of physicians each, indicating moderate levels of treatment resistance in these ranges.
- About 25.93% of physicians observed that more than 30% of patients do not respond to topical treatments, highlighting significant resistance in some cases.

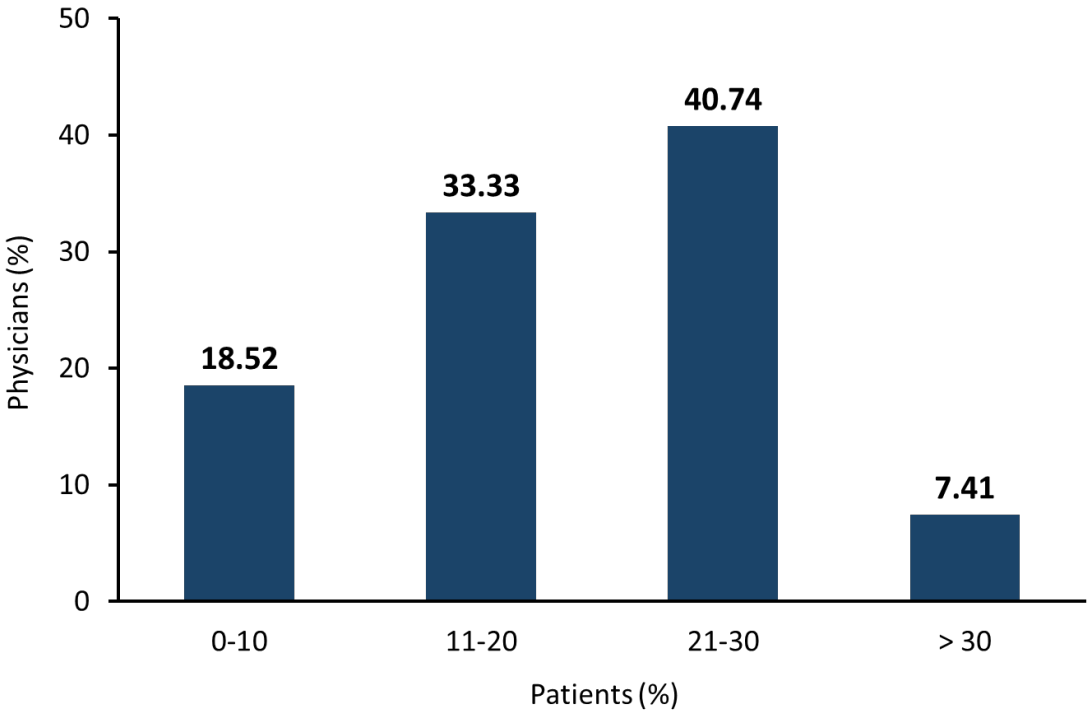
[10] How many percentages of HD CKD pruritus patients does not respond to antihistaminic treatment?

a. 0-10%

b. 11-20%

c. 21-30%

d. >30%

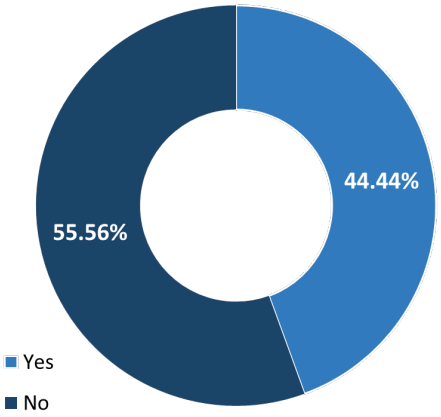


- According to 18.52% of physicians, 0-10% of HD CKD pruritus patients do not respond to antihistaminic treatment, indicating a relatively low non-response rate.
- A larger group of physicians (33.33%), reported that 11-20% of patients fail to respond to these treatments.
- The majority of physicians (40.74%), stated that 21-30% of patients experience no improvement with antihistaminic, highlighting a significant non-response group.
- Only 7.41% of physicians indicated that more than 30% of patients were unresponsive, suggesting this level of treatment resistance is uncommon.

[11] Do you prescribe gabapentin in HD CKD –associated pruritus?

a. Yes

b. No



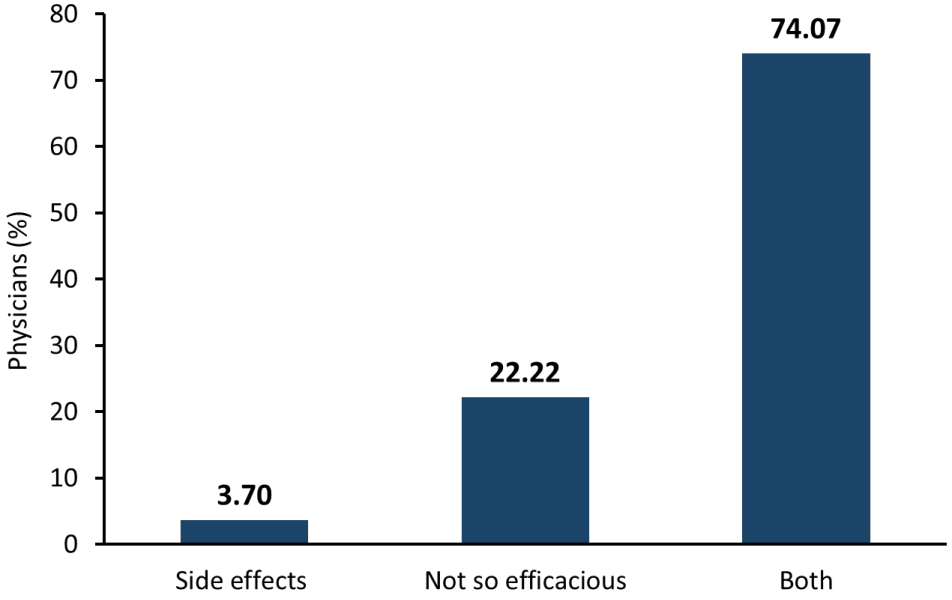
- Gabapentin is prescribed by 44.44% of physicians for managing HD CKD-associated pruritus, indicating it is a common option.
- The majority (55.56%) of physicians, reported that they do not use gabapentin for this condition.

[12] What are drawbacks with currently available treatment in patients with HD CKD –associated pruritus?

a. Side effects

b. Not so efficacious

c. Both



- The majority (74.07%) of physicians, indicated that both side effects and limited efficacy are significant concerns.
- Approximately 22.22% of physicians reported that the treatments are not sufficiently efficacious for managing pruritus in these patients.
- A small percentage of physicians (3.70%) cited side effects as a major drawback of current treatments for HD CKD-associated pruritus.

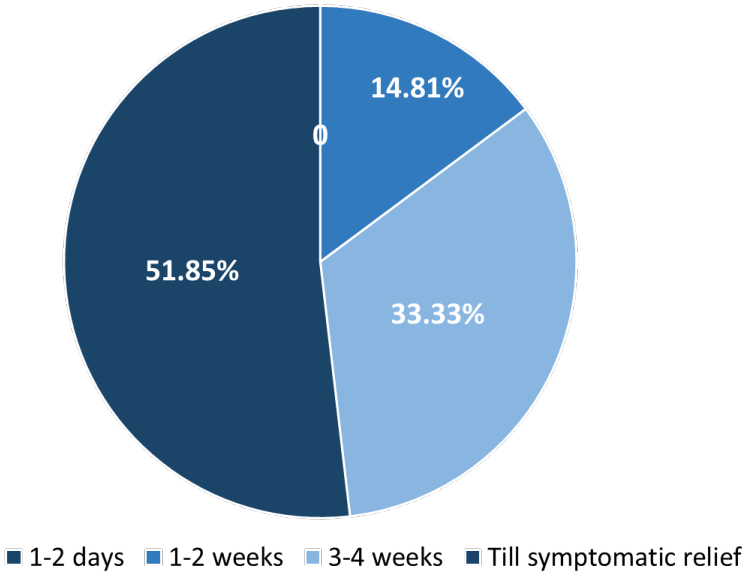
[13] In your clinical practice, how long you prescribe treatment in HD CKD – associated pruritus?

a. 1-2 days

b. 1-2 weeks

c. 3-4 weeks

d. Till symptomatic relief



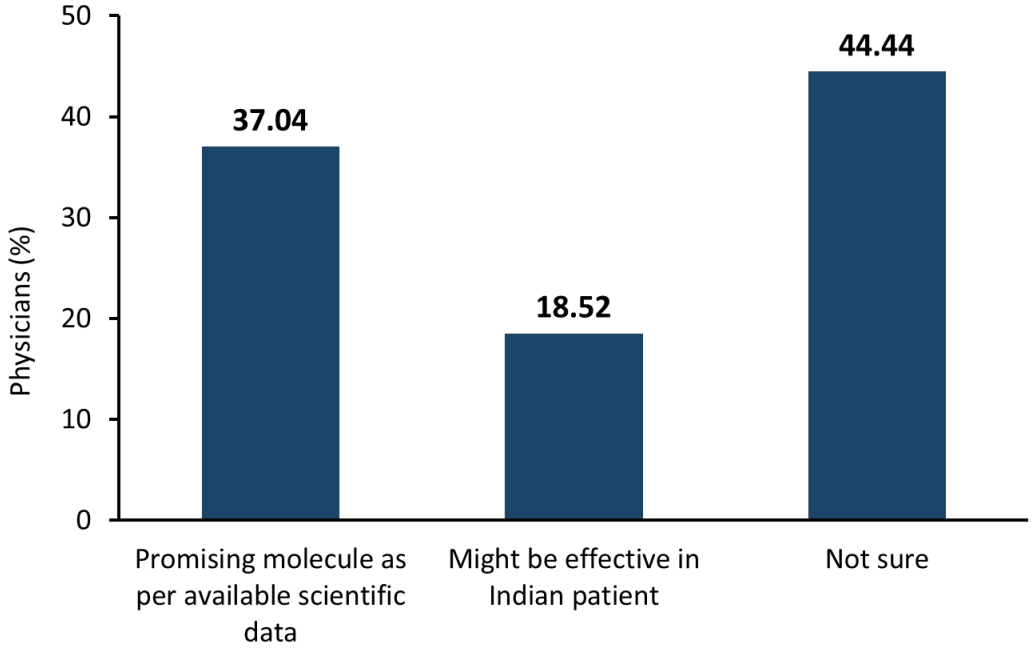
- The majority (51.85%) of physicians prescribed treatment until the patient achieves symptomatic relief, highlighting a patient-centered approach to managing pruritus.
- About one-third of physicians, 33.33%, recommended treatment for 3-4 weeks, suggesting this is a common practice.
- A small group (14.81%) of physicians, typically prescribe treatment for 1-2 weeks.
- None of the physicians reported prescribing treatment for HD CKD-associated pruritus for just 1-2 days, indicating this duration is not considered effective.

[14] What is your view on Difelikefalin in patients with HD CKD –associated pruritus?

a. Promising molecule as per available scientific data

b. Might be effective in Indian patient

c. Not Sure



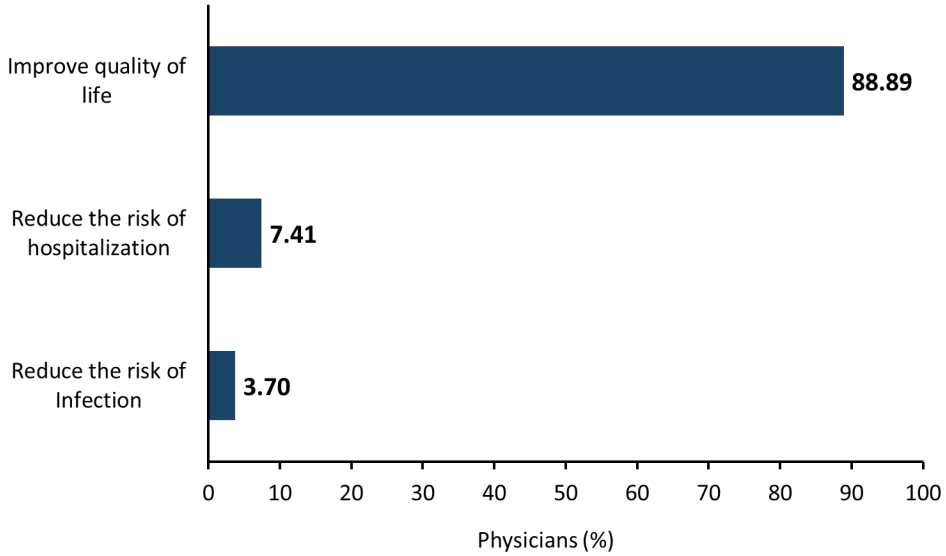
- About 37.04% of physicians observed that difelikefalin as a promising molecule based on the available scientific data for treating HD CKD-associated pruritus.
- Approximately 18.52% of physicians believe it might be particularly effective in Indian patients, suggesting a potential regional variation in its efficacy.
- About 44.44% of physicians were uncertain about difelikefalin's effectiveness, indicating a lack of consensus on its use.

[15] In your opinion, what are the benefits of treating pruritus in patients with CKD?

a. Improve quality of life

b. Reduce the risk of Infection

c. Reduce the risk of Hospitalization



- The majority of physicians (88.89%) believed that treating pruritus in CKD patients significantly improves their quality of life.
- A small group (3.70%) of physicians see treatment as a way to reduce the risk of infections related to pruritus.
- Only 7.41% of physicians believed that treating pruritus can reduce the risk of hospitalization.

6. SUMMARY

A survey of physicians on the management of pruritus in HD patients with CKD revealed key insights into the prevalence, symptoms, diagnosis, treatment approaches, and challenges associated with this condition. Approximately 44.44% of physicians reported that pruritus affected 21–30% of their HD patients, with 29.63% observing it in 11–20% of patients. In terms of symptoms, 77.78% of physicians noted itching, skin sores, and infections as the most common signs of CKD-associated pruritus, though 74.07% emphasized that pruritus can occur even without visible skin abnormalities. Xerosis was identified as a frequent factor, with 88.89% of physicians agreeing on its association with pruritus.

For diagnosis, 55.56% of physicians preferred a combined approach of skin examination and lab investigations, while 33.33% relied on skin examination alone. Treatment strategies were also multifaceted, with 55.56% of physicians opting for a multimodal approach, combining various treatments. Topical treatments, such as emollients and steroids, were the most commonly chosen (29.63%), while systemic treatments like antihistamines and gabapentinoids were less frequently used. Hydroxyzine was the preferred antihistamine for managing pruritus, selected by 59.26% of physicians. However, a significant challenge in treatment was the noted resistance, with 33.33% of physicians reporting that more than 30% of patients did not respond to available treatments.

Treatment durations varied, with 51.85% of physicians prescribing until symptomatic relief was achieved, and 33.33% recommending 3-4 weeks of treatment. The use of gabapentin for pruritus management was common among 44.44% of physicians, although many (74.07%) cited concerns about side effects and limited efficacy. On the promising new treatment difelikefalin, 37.04% of physicians saw it as a potential solution, although 44.44% remained uncertain about its effectiveness. Overall, 88.89% of physicians agreed that treating pruritus significantly improves the quality of life for CKD patients, highlighting the importance of effective management.

7. DISCUSSION

The results of the survey provide valuable insights into the prevalence, diagnosis, treatment approaches, and challenges associated with managing pruritus in HD patients with CKD. A significant portion of physicians, 44.44%, observed that pruritus affects 21-30% of their HD CKD patients, while 29.63% noted a prevalence of 11-20%, indicating that pruritus is a common issue in this population. In contrast, only a small group (3.70%) reported a low prevalence, suggesting that pruritus is an underrecognized condition for some healthcare providers.

When considering the symptoms of CKD-associated pruritus, itching, skin sores, and skin infections were the most frequently observed, with 77.78% of physicians reporting these signs. Interestingly, no physicians identified skin sores as a symptom, while skin infections were seen by a small proportion (3.70%) of physicians. The majority of physicians (74.07%) confirmed that pruritus could occur even in the absence of visible skin abnormalities, while 25.93% disagreed, highlighting varying perceptions on the nature of pruritus in this patient group. Additionally, xerosis was identified as a commonly associated factor by 88.89% of physicians, underscoring its relevance in the pathophysiology of CKD-related pruritus. Regarding diagnosis, a combined approach of skin examination and lab investigations was preferred by 55.56% of physicians, while 33.33% relied solely on skin examination. This suggests that a multimodal diagnostic approach is common in clinical practice. Treatment strategies also varied, with the majority (55.56%) favoring a multimodal approach combining different treatment options. Topical treatments, such as emollients and steroids, were the most commonly used, selected by 29.63% of physicians, while systemic treatments like antihistamines and gabapentinoids were less commonly prescribed. Nonpharmacological therapies, such as phototherapy and acupuncture, were not widely utilized.

When it comes to treatment efficacy, a significant proportion of physicians reported treatment resistance among their patients. Approximately 33.33% of physicians indicated that more than 30% of their patients did not respond to available treatments, highlighting the difficulty in achieving satisfactory relief for many patients. The most preferred antihistamine for pruritus treatment was hydroxyzine, chosen by 59.26% of physicians, followed by cetirizine (25.93%) and chlorpheniramine maleate (14.81%). However, concerns regarding limited efficacy and side effects were noted

by 74.07% of physicians, with 22.22% highlighting insufficient efficacy as a major concern. A patient-centered approach was reflected in the treatment duration, with the majority (51.85%) of physicians prescribing treatment until symptomatic relief was achieved. However, about 33.33% recommended treatment for 3-4 weeks, and only 14.81% prescribed it for 1-2 weeks. These findings suggest that physicians aim for flexible, patient-tailored treatment regimens. Moreover, a promising new molecule, difelikefalin, was considered a potential treatment option by 37.04% of physicians, although 44.44% were uncertain about its efficacy, indicating the need for further research and consensus.

Finally, physicians overwhelmingly agreed that treating pruritus in CKD patients significantly improves their quality of life (88.89%), emphasizing the importance of symptom management. However, the perceived impact of pruritus treatment on reducing infection risk and hospitalizations was less certain, with only 3.70% and 7.41% of physicians indicating these benefits, respectively. This highlights the multifaceted impact of pruritus and the need for continued research and more effective management strategies to improve patient outcomes in this challenging clinical scenario.

8. CLINICAL RECOMMENDATIONS

Based on the survey results, it is evident that pruritus in HD patients with CKD is a prevalent and challenging condition for many physicians. A significant proportion of physicians (44.44%) report that pruritus affects 21-30% of their HD patients, with others indicating that a large number of patients (29.63%) experience pruritus in the 11-20% range. This suggests that CKD-associated pruritus is a common and persistent issue in clinical practice. Furthermore, the majority of physicians (74.07%) agree that pruritus can occur even in the absence of skin abnormalities, underscoring the complexity of diagnosis and the need for a comprehensive approach that combines both clinical examination and laboratory investigations.

In terms of treatment, a multimodal strategy appears to be the most favored, with 55.56% of physicians recommending a combined approach using all available therapies. Topical treatments such as emollients, topical analgesics, and steroids are commonly used, while systemic treatments like antihistamines and gabapentinoids are less frequently employed. Hydroxyzine is the most commonly prescribed antihistamine, and gabapentin is widely used, though a notable proportion of physicians (55.56%) do not prescribe it. Despite these efforts, treatment resistance remains a significant challenge, with approximately 33.33% of physicians reporting that over 30% of patients fail to respond to available treatments.

To optimize management, physicians should continue to prioritize individualized treatment plans, particularly focusing on combinations of topical and systemic therapies, with consideration given to the potential for side effects and limited efficacy of current treatments. Special attention should be given to emerging therapies like difelikefalin, with 37.04% of physicians recognizing its potential, although a lack of consensus on its effectiveness exists. Given the significant impact on patient quality of life, it is crucial to address pruritus early and adjust therapies as needed, keeping in mind that patient-centered care, with treatment tailored to symptom relief, is a critical aspect of management. Additionally, further research into the efficacy of treatments like difelikefalin, as well as regional variations in response, will be important for improving outcomes in this patient population.

9. CONSULTING OPINION

Based on the collected data, it is evident that pruritus is a common and significant issue in patients undergoing HD for CKD. The majority of physicians observe that pruritus affects a substantial portion of their patients, with 44.44% noting it impacts 21-30% of HD CKD patients. Notably, 33.33% of physicians report that over 30% of patients do not respond to available treatments, highlighting a major challenge in managing this condition. While topical treatments, including emollients, corticosteroids, and tacrolimus, are commonly used, systemic treatments like antihistamines, gabapentinoids, and opioids are less frequently prescribed. Despite this, hydroxyzine emerges as the preferred antihistamine for managing pruritus in this population.

There is a clear preference for a combined approach in diagnosing CKD-associated pruritus, with most physicians opting for a combination of skin examination and lab investigations. Furthermore, while the majority acknowledge that pruritus can occur even in the absence of visible skin abnormalities, xerosis (dry skin) is considered a common associated factor. Interestingly, difelikefalin, a promising treatment, is viewed with uncertainty by many physicians, with a significant proportion unsure about its effectiveness. The data also underscores the importance of a patient-centered approach, with most physicians prescribing treatments until symptomatic relief is achieved. However, concerns regarding the efficacy and side effects of available treatments remain prevalent, with over 70% of physicians indicating that these issues are significant barriers to optimal management. Despite the challenges, most physicians recognize that effective management of pruritus can substantially improve the quality of life for CKD patients, emphasizing the importance of continued research and innovation in treatment options.

10. MARKET OPPORTUNITIES

The results from the survey highlight several key opportunities for marketing in the treatment of CKD-associated pruritus, particularly in the HD patient population. A significant portion of physicians (44.44%) observe pruritus in 21–30% of HD CKD patients, indicating a substantial unmet need for effective treatments. With a high prevalence of symptoms like itching, skin sores, and skin infections, and the majority of physicians confirming that pruritus can occur without visible skin abnormalities, there is a clear demand for comprehensive diagnostic tools and treatments that address both the symptomatic and underlying causes of pruritus.

Given that 55.56% of physicians favor a combined approach to diagnosis and treatment, marketing efforts could focus on offering multimodal therapies that integrate both topical and systemic options, such as emollients, antihistamines, and gabapentinoids. Furthermore, the relatively high non-response rates (29.63% of physicians report that 21–30% of patients do not respond to current therapies) present an opportunity to introduce more effective treatments, especially in light of the significant concerns over the limited efficacy and side effects of current options. A promising molecule like difelikefalin, which is seen as a potential treatment by 37.04% of physicians, could be marketed more aggressively, with a focus on its efficacy and ability to improve quality of life. Furthermore, emphasizing the role of pruritus treatment in improving the quality of life (88.89% of physicians agree on this benefit) and potentially reducing the risk of infections could resonate with healthcare providers seeking better patient outcomes. Finally, the varying response to treatments in different regions suggests an opportunity to tailor marketing strategies, particularly in countries like India, where 18.52% of physicians believe difelikefalin may be particularly effective. This regional approach could enhance treatment adoption and address the diverse needs of the global CKD patient population.

11. MARKET POSITIONING

A pressing need for effective treatment options for pruritus in HD-CKD patients, as a significant number of physicians (33.33% to 74.07%) express concerns about treatment resistance and limited efficacy. Despite the availability of treatments such as antihistamines, gabapentin, and topical therapies, substantial levels of non-responsiveness (21-30% and more than 30% of patients) indicate a considerable unmet need for more effective and widely accepted solutions. Additionally, 74.07% of physicians emphasize concerns over side effects and the limited effectiveness of current treatments.

Given these insights, a market positioning strategy should prioritize delivering a treatment that addresses these challenges—one that offers higher efficacy, fewer side effects, and a more consistent response for HD CKD patients. While newer options like difelikefalin show promise, they lack universal acceptance, pointing to a need for further clinical evidence and physician education to boost confidence. Marketing should focus on the potential to significantly enhance patients' quality of life, as noted by 88.89% of physicians. Offering flexible treatment regimens, ranging from 1-2 weeks to longer durations, will align with physicians' preference for patient-centered care approaches. Ultimately, the positioning strategy should highlight the availability of a comprehensive, effective, and safe solution for managing CKD-associated pruritus, supported by strong scientific evidence, and adaptable to varying regional needs and treatment preferences.

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