Treatments for Uremic Pruritus

Subjects: Dermatology
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Conventional treatments for uremic pruritus including emollient, topical agents, antihistamine, dialysis modification, phototherapy, and serotonin receptor antagonists.

uremic pruritus | chronic kidney disease associated pruritus | chronic pruritus

1. Moisturizers

Xerosis is found in 50–85% of patients with uremic pruritus and is an aggravating factor of pruritus [1]. Multiple trials using different emollients including glycerol and paraffin, 10% urea and dexpanthenol, physiological lipids, and baby oil decrease xerosis and pruritus in patients with uremic pruritus [2][3][4][5][6]. Emollient is suggested as first-line therapy in patients with uremic pruritus, especially for those with less severity [7].

2. Topical Calcineurin Inhibitor (Tacrolimus, Pimecrolimus)

Tacrolimus, a calcineurin inhibitor, is used for its anti-inflammatory effects in atopic dermatitis and vitiligo [8][9]. A case study reported that 0.03% tacrolimus ointment reduced pruritus intensity in three cases with severe uremic pruritus [10]. However, a randomized, double-blind, vehicle-controlled study demonstrated that 0.1% tacrolimus applied twice daily for 4 weeks was not more efficacious than the vehicle [11]. Another 8-week, randomized, double-blind study of 1% pimecrolimus also revealed a lack of efficacy compared to the placebo group [12].

3. Other Topical Agents

Capsaicin, a compound found in chili pepper and transient receptor potential vanilloid member 1 (TRPV1) agonist, was used to relieve pain and neuropathy [13]. Three randomized controlled trials of capsaicin cream for uremic pruritus showed limited efficacy [14]. Pramoxine is a topical anesthetic with antipruritic effects. A randomized, double-blind, controlled comparative trial with 28 patients using 1% pramoxine lotion showed a 61% decrease in pruritus intensity compared to 12% in the placebo group [15].

4. High Quality of Dialysis

Since uremic toxins are suggested as potential pruritogens, increasing the efficiency of dialysis and modification of hemodialysis prescription is a potential strategy for the treatment of uremic pruritus. One randomized trial found that increased dialysis efficiency with mean Kt/V up to 1.28 resulted in pruritus improvement compared to mean

Kt/V of around 1.09 [16]. Dialysis modification to remove more middle molecules also showed improvement in pruritus intensity. Hemodialysis modifications including high-flux hemodialysis [17], hemodiafiltration with hemodialysis [18], and high-permeability hemodialysis [19] have shown significant decreases in pruritus intensity. Therefore, increasing dialysis efficiency as well as modulating dialysis parameters are suggested as first-line treatments in patients with uremic pruritus [20].

5. Phototherapy

Phototherapy has been widely used in inflammatory skin diseases such as psoriasis, atopic dermatitis, and vitiligo [8][9][21] by modulating Th1 and Th2 lymphocyte differentiation and attenuating Th1-mediated responses [22][23]. Broadband ultraviolet B phototherapy was found to be effective in patients with uremic pruritus compared to ultraviolet A phototherapy [24]. One single-blind, randomized, controlled trial of 21 patients with uremic pruritus showed a significant improvement in pruritus by narrowband ultraviolet B phototherapy and long-wave ultraviolet A phototherapy compared to the non-treated group [22]. A recent controlled trial of narrowband ultraviolet B phototherapy revealed a significant reduction in visual analog scale (VAS) from 9.1 to 1.9 compared to treatment with antihistamine and emollients. In addition, the effect was sustained for up to 6 months in most of the study group [25]. Due to its wide adoption in pruritic dermatoses, narrowband ultraviolet B is considered an efficacious treatment in uremic pruritus.

6. Antihistamine

Antihistamine, mainly targeting histamine H1 receptor, has been widely used for anti-pruritus. It has been reported that over half of physicians prescribed an oral anti-histamine and one-fourth of them prescribed a topical anti-histamine as first-line therapy for uremic pruritus; however, anti-histamines were generally unsatisfactory for the treatment of uremic pruritus [7][26][27]. In addition, side effects of anti-histamines such as dizziness, sedation, and urine retention are concerns in patients with CKD [7].

7. Gabapentin, Pregabalin

Both pregabalin and gabapentin, analogs of gamma-aminobutyric acid, are modulators of neurotransmitters, acting possibly by decreasing neurotransmitter release [28]. The neuropathic role was implicated in the pathogenesis of various pruritic disorders such as brachioradial pruritus and pruritus in patients with diabetic neuropathic pain [29]. Several clinical trials of gabapentin and pregabalin have shown them to be statistically significant in the reduction in pruritus intensity in patients with uremic pruritus [30][31][32][33]. One recent systematic review showed decreased severity of pruritus after treatment with gabapentin in four out of seven studies (n = 171). Incidences of adverse effects with gabapentin including dizziness, drowsiness, and somnolence were higher but not significant in a pooled analysis (n = 290) [34]. Another clinical trial demonstrated that pruritus was relieved in 85% of 71 patients by gabapentin or pregabalin and that patients intolerant to gabapentin might tolerate pregabalin [35]. One study comparing the effects of gabapentin after each dialysis session and pregabalin daily showed a significant

improvement in the reduction in pruritus and neuropathic pain in both groups [33]. A systematic review concluded that gabapentin is the most reliable and effective treatment as an off-label treatment for uremic pruritus [36].

8. Opioid Receptor Agonist/Antagonist

8.1. Naloxone

Intravenous injection of naloxone, a mu-receptor antagonist, was firstly reported to be efficacious in treating uremic pruritus in 1984 [37]. However, inconsistent results were found in subsequent large studies of oral naltrexone for uremic pruritus. In addition, some studies revealed frequent adverse effects such as nausea and sleep disturbance [38][39][40].

8.2. Nalfurafine

Nalfurafine, a selective kappa agonist, was found to be effective in uremic pruritus in a multicenter, randomized, double-blind, placebo-controlled clinical study [41]. A phase III randomized, double-blind, placebo-controlled study of 337 patients also revealed that nalfurafine significantly reduce the itch severity in intractable uremic pruritus [42]. Nalfurafine was officially approved for clinical use for uremic pruritus in Japan.

8.3. Difelikefalin

Recently, difelikefalin, a peripheral restricted and selective kappa opioid receptor agonist, proved its efficacy in the treatment of uremic pruritus in a large double-blind, placebo-controlled, multicenter phase III trial [43]. A total of 378 hemodialysis patients with moderate to severe pruritus were randomly treated with intravenous difelikefalin at the dose of 0.5 μg per kilogram or placebo for 12 weeks. Difelikefalin significantly decreased the intensity of pruritus (at least 3 points from baseline according to a 24-h worst itching intensity numerical rating scale) in 51.9% of patients compared to 30.9% of patients in the placebo group. Itch-related quality of life also improved significantly compared to the placebo group. Common adverse events include diarrhea, dizziness, and vomiting, but no adverse events of dysphoria, hallucination, euphoria, or discontinuation-related discomfort were reported in the difelikefalin group. Based on the successful results of the phase III trial, difelikefalin was approved by the FDA in the United States in 2021. A regulatory review is ongoing in Europe and a phase III trial is in progress in Japan. Oral difelikefalin is under investigation [44].

8.4. Nalbuphine

Nalbuphine, a combination of kappa-opioid receptor antagonist and mu-opioid receptor agonist, has been reported to be beneficial for morphine-related itch [45]. In addition, nalbuphine also decreased the intensity of uremic pruritus [46]. A multicenter, randomized, double-blind, placebo-controlled trial of 373 hemodialysis patients with moderate to severe pruritus demonstrated that the group receiving nalbuphine 120 mg twice daily for 8 weeks reported significantly decreased pruritus. However, there was no significant difference between nalbuphine at the dose of 60 mg twice daily and the placebo group.

9. Mast Cell Stabilizer

Mast cell stabilizers, which prevent degranulation of inflammatory mediators from mast cells, have been shown to be effective in uremic pruritus, and include topical cromolyn sodium [47], oral cromolyn sodium [48], ketotifen [31], and zinc sulfate [49]. One double-blind, randomized clinical trial of 52 patients revealed similar efficacy in decreasing pruritus severity and no significant difference in adverse effect with gabapentin and ketotifen [31]. However, one randomized control trial of 36 patients with 4-week duration of zinc sulfate showed non-significant reduction in pruritus in hemodialysis patients [50]. Mast cell stabilizer is safe and potentially efficacious in uremic pruritus, but more studies are needed.

10. Montelukast

Leukotriene B4, primarily released by macrophage and leukocytes, is involved in itch and may induce scratching [51][52]. Montelukast, a leukotriene receptor antagonist, is used in atopic dermatitis, asthma, allergic rhinitis, and idiopathic urticaria. One randomized double-blind controlled trial of 80 hemodialysis patients receiving 10 mg montelukast daily for 30 days revealed that montelukast significantly decreased pruritus compared to the placebo group. The authors concluded that montelukast might serve as an add-on treatment in intractable uremic pruritus [53].

11. Serotonin Receptor Antagonist: Ondansetron

5-HT3 receptor antagonists have been studied for their treatment efficacy in uremic pruritus. Ondansetron, a selective 5-HT3 receptor antagonist, had an insignificant effect on uremic pruritus in two randomized controlled trials [54][55].

12. Nemolizumab

Due to the higher concentration of IL-31 in hemodialysis patients with uremic pruritus, the role of nemolizumab, an IL-31 receptor alpha antibody, in the treatment of uremic pruritus is suggested [56]. A randomized, double-blind, placebo-controlled phase IIB trial of a single dose of nemolizumab was conducted in 69 patients with uremic pruritus but failed to meet the primary efficacy endpoint [57].

13. Dupilumab

As the possible involvement of IL-31 was implicated in uremic pruritus, the role of T-helper 2, which is the upstream regulator of IL-31, in uremic pruritus has been suggested. Dupilumab, an IL-4 receptor alpha-blocker, was reported to successfully treat cases with intractable uremic pruritus [58][59]. More studies are necessary.

14. Acupuncture, Acupressure

Acupuncture, defined by acupuncture needle insertion into specific points of the skin as treatment, has long been used for a variety of symptoms, such as acute or chronic pain, sleep disturbance, and poor quality of life in East Asia [60]. Acupuncture was believed to act through modulating the endogenous opioid system [61], which accounts for the hypothesis of it treating uremic treatment. Similarly, acupressure stimulates the acupuncture points with body parts of practitioners or designed equipment. A systematic review including six trials showed that acupuncture and acupressure were effective for uremic pruritus [62]. Recent studies comparing Zolpidem and acupressure revealed that both improved sleep quality and quality of life in patients with uremic pruritus-associated sleep disturbance [63][64]. However, more evidence is needed to affirm this as a recommended treatment for uremic pruritus.

15. Charcoal

Given the hypothesis of non-dialyzable uremic toxins as possible pruritogens, the adequate removal of potential toxins by charcoal is a reasonable therapeutic option. Activated charcoal, a non-selective absorbent, is usually used for detoxication in certain kinds of poisoning. An 11-patient, placebo-controlled, double-blind, crossover study showed that a daily dose of 6 g of activated charcoal for 8 weeks decreased pruritus in most patients with uremic pruritus [65]. In addition, coated charcoal in extracorporeal techniques showed decreased levels of parathyroid hormone and pruritus in a study of 12 patients [66]. Although evidence with large case numbers and well-designed studies are lacking, a recent review showed a promising role of charcoal in uremic pruritus [67].

16. Other Treatment

Early studies have proposed the association of uremic pruritus with hyperthyroidism, calcium, and phosphate. It is reported that the level of calcium multiplied by phosphate is correlated with the extent of pruritus after parathyroidectomy, and intractable pruritus improved after parathyroidectomy in some cases [68][69].

Thalidomide, an immunomodulator and neuromodulator, was initially observed to reduce pruritus in dialysis patients with leprosy [70]. One early randomized, crossover study with 29 patients found a statistically significant decrease in pruritus in the thalidomide group [71].

Gamma-linolenic acid (GLA), an essential acid, is thought to modulate T lymphocytes and lymphokines. In one small-sized, randomized control trial, GLA-enriched cream significantly improved the pruritus severity in dialysis patients [72].

Cannabinoids act on the endocannabinoid system to modulate pruritus and shed light on the treatment of chronic and refractory pruritus with legalized medical marijuana [73]. In a study of 21 patients applying topical cream containing structured physiological lipids, anandamide, and palmitoylethanoamine twice daily for 3 weeks, 8 out of 21 patients with uremic pruritus were completely free from pruritus [3]. However, randomized trials for cannabinoids are lacking [74].

Kidney transplantation, a kidney replacement therapy, largely decreased or cured chronic pruritus in patients with uremic pruritus [20][75][76]. Other medical considerations remain issues due to the shortage of human kidneys.

Catabolism of exogenous protein may lead to the retention of protein-bound molecules. Therefore, protein-restrictive diets and probiotics may serve as a potential treatments for uremic pruritus [67]. Omega-3 supplements were found to be effective to decrease pruritus in a cross-randomized trial [77].

Table 1. Summary of studies of interventions for uremic pruritus.

Authors	Study Design	Participants	Enrollment	Intervention	Comparator	Efficacy
Duque et al. (2005) [11]	Randomized, double-blind, vehicle-controlled study	HD	N = 22	0.1% tacrolimus ointment twice daily for 4 weeks	Vehicle	No significant effect.
Ghorbani et al. (2011) [12]	Randomized double-blind study	Not mentioned	N = 60	Pimecrolimus 1% twice daily for 8 weeks	Placebo	No significant effect.
Ko et al. (2011) [22]	Single-blind, randomized, controlled trial	HD, PD, CKD	N = 21	NB-UVB phototherapy three times a week for 6 weeks	Long-wave UVA radiation	Significant and comparable improvement in the VAS scores in both groups.
Sherjeena et al. (2017) [25]	Controlled trial	CKD, stage IV, V	N = 30	NBUVB phototherapy every 3 days for 15 sessions	Topical liquid paraffin, 10 mg oral cetirizine daily	Significant effect. VAS 9.13 to 1.9 at 3 months (NBUVB). VAS 9.1 to 8.8 at 3 months (control).
Mapar et al. (2015) [50]	Pilot randomized, triple-blind study	HD	N = 36	Zinc sulfate 220 mg daily for 4 weeks	Placebo	No significant effect.
Mahmudpour et al. (2017) [53]	Randomized double-blind controlled trial	HD	N = 80	Montelukast 10 mg daily for 30 days	Placebo	Reduction in VAS score was significantly greater in the

Authors	Study Design	Participants	Enrollment	Intervention	Comparator	Efficacy
						montelukast group (2.73) compared to placebo group (5.47).
Amirkhanlou (2016) [31]	Double-blind randomized clinical trial	HD	N = 52	Gabapentin 100 mg daily for 2 weeks	Ketotifen 1 mg twice daily for 2 weeks	Significant reduction in both groups (88.4% in gabapentin group vs. 76.9% in group ketotifen group).
Eusebio-Alpapara et al. (2020) [34]	Meta-analysis	HD	N = 315	Gabapentin 100 mg daily, 100–400 mg 2–4 times per week	Antihistamine, pregabalin, placebo	Gabapentin decreased the pruritus severity compared to the placebo (*n* = 171).
Kumagai et al. (2010) [42]	Randomized, double-blind, placebo-controlled study	HD	N = 337	Nalfurafine hydrochloride 5 µg, 2.5 µg for 14 days	Placebo	Significant reduction in VAS in both dosages of nalfurafine compared to placebo.
Mathur et al. (2017) [46]	Randomized, double-blind, placebo-controlled trial	HD	N = 373	Nalbuphine 120 mg, 60 mg twice daily for 8 weeks	Placebo	Significant effect with nalbuphine 120 mg, but not with nalbuphine 60 mg.
Fishbane et al. (2020) [43]	Double-blind, placebo-controlled, phase III trial	HD	N = 378	Intravenous difelikefalin 0.5 µg per kilogram per week for 12 weeks	Placebo	A decrease of at least 3 points (WI-NRS score) in 49.1% of the difelikefalin group (27.9% of the placebo group).

References

Authors	Study Design	Participants	Enrollment	Intervention	Comparator	Efficacy
Kinugasa et al. (2021) [57]	Randomized, double-blind, placebo-controlled clinical study	HD	N = 69	Nemolizumab 0.125, 0.5, 2.0 mg/kg on day 1	Placebo	No significant effect.

HD, hemodialysis; PD, peritoneal dialysis; CKD, chronic kidney disease; VAS, visual analog scale; NB, narrow band; WI-NRS, worst itch numeric rating scale. The data were retrieved by 25 March 2022.

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