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Efficacy and Tolerance of the Cream Containing Structured Physiological Lipids with Endocannabinoids in the Treatment of Uremic Pruritus: A Preliminary Study

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SUMMARY Uremic pruritus is still a common phenomenon in patients with end-stage renal failure, however, there is no effective treatment of choice for this condition.This study was undertaken to evaluate the efficacy and tolerance of the cream with structured physiological lipids (DMS®, Derma Membrane Structure®) and endogenous cannabinoids in controlling pruritus in patients on maintenance hemodialysis. Twenty-one subjects with uremic pruritus completed the trial. All patients applied the tested cream twice daily for a period of three weeks. Pruritus was evaluated using two pruritus scoring methods: standard visual analog scale (VAS) and a questionnaire method. Moreover, all patients had dry skin scored according to the 5-point scale. Global pruritus and xerosis were examined before the trial, on study visits at weekly intervals, and on follow-up visit performed two weeks of study discontinuation.
After 3-week therapy pruritus was completely eliminated in 8 (38.1%) patients. Pruritus evaluation by both scales revealed significant reduction of pruritus scores ($p<0.0001$) during the tested product application. At the beginning of the trial there was no significant correlation between the intensity of dry skin and severity of pruritus. The 3-week treatment period resulted in complete reduction of xerosis in 17 (81%) patients, while xerosis scores were significantly reduced ($p=0.0001$) throughout the study period. The test product was very well tolerated by all patients.The test product appeared to be effective in reducing both pruritus and xerosis in hemodialysis patients. It is very probable that the observed decrease of pruritus with the test product therapy was not only the result of dry skin improvement but that the addition of endocannabinoids may have also played a role. These preliminary results are encouraging, however, additional controlled studies are needed to clarify the exact usefulness of this product in therapy of uremic pruritus.

KEY WORDS: uremic pruritus; xerosis; hemodialysis; endocannabinoids

INTRODUCTION

Uremic pruritus is still a common phenomenon in patients with end-stage renal failure (1,2). It is regarded as one of the most bothersome symptoms in patients on maintenance hemodialysis. The etiopathogenesis of uremic itch remains unclear. Several theories and hypotheses have been proposed, including dryness of the skin, mast cell accumulation, disturbance in tryptase and chymase activity, imbalance in divalent ions, peripheral neuropathy and opioid system involvement (reviewed

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in ref. 3). As the pathogenesis of this symptom has not yet been fully elucidated, there is no treatment of choice for these patients. Many treatment modalities have been tried to reduce uremic pruritus, however, the majority of them produced insufficient and only temporary improvement (reviewed in ref. 4). Therefore, every new therapeutic option for uremic pruritus is desirable.

This study was undertaken to evaluate the efficacy of a cream with structured physiological lipids (DMS®, Derma Membrane Structure®) and endogenous cannabinoids in controlling pruritus in patients on maintenance hemodialysis, and to assess local tolerance and patient acceptability of the test product in the study population. Moreover, we evaluated the efficacy of the tested cream for possible xerosis in chronic hemodialysis patients.

PATIENTS AND METHODS

Patients

At the beginning 23 patients on maintenance hemodialysis suffering from uremic pruritus were included in the study. One patient refused to continue the trial just after one day of the test product application, without giving the reason for this (no adverse effects were observed). The next one died from slowly increasing hyperkaliemia two weeks of starting the trial. So, 21 patients (10 female and 11 male) completed the trial. Their age ranged from 31 to 81, mean 58 years. They had been on hemodialysis for 0.5 to 17, mean 4.2 years. The reasons for chronic renal insufficiency in these patients were as follows: chronic glomerulonephritis (n=8), diabetic nephropathy (n=6), interstitial nephritis (n=3), polycystic kidney disease (n=2) and nephropathy due to arterial hypertension (n=2). All patients were hemodialyzed 3 times a week for 4 hours using bicarbonate-based dialysate. Polysulphone membranes were used in 19 and cuprophane membranes in the remaining two patients. All patients suffered from uremic itch. The duration of pruritus varied from one month to 17 years, mean 2.7 years. In six patients the intensity of pruritus increased during the hemodialysis procedure, in one subject just after hemodialysis; in the remaining 14 patients the intensity of pruritus did not depend on hemodialysis sessions. Seven patients had previously tried to reduce their pruritus using oral anihistaminics (n=6) or topical moderately potent corticosteroids (n=1), without any marked clinical improvement. None of the patients had used any antipruritic treatment such as emollients for at least 4 weeks before the trial.

Methods

All patients underwent careful dermatologic examination to diagnose uremic pruritus. They all applied the cream with structured natural lipids (DMS®) containing endocannabinoids: N-acetylethanolamine (AEA) and N-palmitoylethanolamine (PEA) (Physiogel AI® cream) twice daily for a period of 3 weeks. Pruritus was evaluated by the same investigators using two pruritus scoring methods: standard visual analog scale (VAS) and questionnaire method, successfully used by our group in several studies on different types of pruritus. This method consisted of the assessment of distribution, frequency and severity of pruritus, and sleep disturbances caused by itching. Details of this measurement are given in Table 1. Moreover, all patients had dry skin scored according to the 5-point scale, as follows:

0 smooth skin
1 patches of fine, powdery scales
2 diffuse ashy appearance with fine scales
3 moderate scaling with beginning cracks
4 intense scaling, moderate cracks

The most dry skin area of the patient's skin was selected for xerosis evaluation. Global pruritus and xerosis were examined before the trial as well as on study visits at weekly intervals and at the follow-up visit performed two weeks of discontinuation of the cream application. Moreover, at the end of the cream usage (3 weeks of application) global tolerance was evaluated by the investigators using the following 4-point scale:

1 very good tolerance
2 good tolerance
3 poor tolerance
4 very poor tolerance

At the same time, global agreement of the patient was evaluated according to the following 4-point scale:

1 very satisfactory
2 satisfactory
3 poorly satisfactory
4 not satisfactory at all

Statistical analysis

Statistical analysis was performed by use of Wilcoxon test and Spearman rank correlation test. Values of p less than 0.05 were considered statistically significant.

RESULTS

Both scales used for pruritus evaluation showed a significant positive correlation (r=0.52; p=0.015). After 3-week therapy, pruritus was completely eliminated in eight (38.1%) patients. During the follow-up period, pruritus reappeared in two of these eight patients but disappeared in another two patients. Thus, at follow-up 14 days of therapy discontinuation eight (38.1%) patients were free from itch.

Evaluation of pruritus by VAS showed significant reduction of pruritus scores during the test product application (Table 2, Fig. 1). Differences in the scores between each two visits were statistically significant. At 14 days of therapy discontinuation pruritus increased significantly in comparison to the assessment made at the end of treatment, however, it was still significantly less intensive than before the treatment.

Table 1. Pruritus score scale

Evaluation	Points
Distribution	
Single area involved	1
Multiple sites of pruritus	2
Generalized pruritus	3
Frequency	
Four short episodes (<10 min)	1
One long (>10 min)	1
(maximum 5 points)	
Severity	
Pruritus without the need to scratch	1
Pruritus with the need to scratch, but without physical signs of excoriations	2
Pruritus unrelieved by scratching, but without excoriations	3
Pruritus accompanied by excoriations	4
Totally restless	5
Sleep disturbance	
Each episode of awakening due to pruritus (maximum 6 points)	2

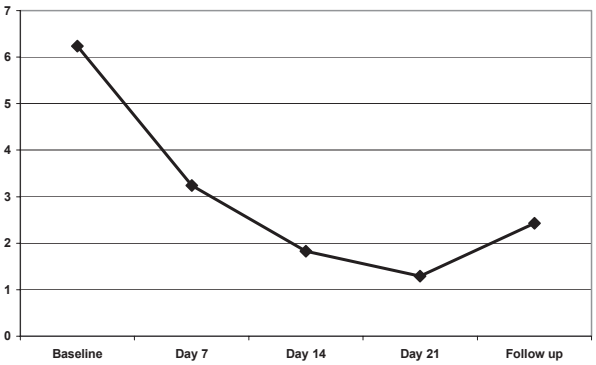

Figure 1. Pruritus scores during therapy (VAS, visual analog scale)

Similar results were observed when pruritus was evaluated by the questionnaire method (Table 2, Fig. 2). Pruritus was significantly reduced on each study visit during the 3-week treatment period, and increased 14 days after therapy discontinuation, however, the difference between day 21 and follow-up visit was not significant. The intensity of pruritus at follow-up visit was still significantly lower compared to the beginning of the trial. Details of statistical analysis are given in Table 3.

Assessment of the elements of pruritus evaluation (distribution, frequency and severity of pruritus, and sleep disturbances) showed all study parameters to significantly decrease during the treatment (Tables 2 and 3, Fig. 3). The scores for sleep disturbances were reduced at a slower rate than those for other parameters, and increased significantly upon discontinuation of the test product usage. This was not observed for the distribution, frequency and severity of pruritus scores.

Xerosis was observed in all study patients. At the beginning of the study, there was no significant correlation between the intensity of dry skin and severity of pruritus as assessed by either scale (VAS: r=0.31, p=0.17; questionnaire: r=0.36,

Table 2. Mean pruritus and xerosis scores during the study

		Baseline (1)	Day 7 (2)	Day 14 (3)	Day 21 (4)	Follow up (5)
Pruritus	VAS	6.24±2.19	3.24±1.87	1.83±1.64	1.29±1.41	2.43±2.82
	Questionnaire					
	- Total scores	9.86±4.69	5.9±3.92	3.86±3.26	2.76±2.41	4.33±5.35
	- Distribution	2.0±0.63	1.38±0.74	1.19±0.87	0.9±0.77	0.86±0.96
	- Frequency	2.9±1.64	1.81±1.4	1.05±0.97	0.76±0.62	1.14±1.42
	- Severity	3.1±1.04	1.76±0.94	1.24±0.89	0.9±0.77	1.38±1.56
	- Sleep disturbances	1.81±2.27	0.95±1.86	0.29±0.96	0.19±0.87	0.95±1.96
Xerosis		1.76±0.94	0.52±0.51	0.24±0.44	0.19±0.4	0.43±0.6

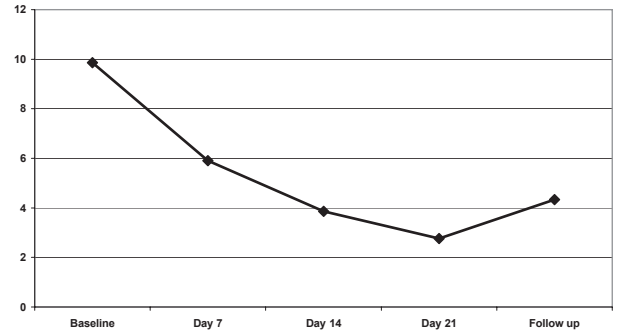

Figure 2. Pruritus scores during therapy by the questionnaire method.

p=0.11). The 3-week treatment period resulted in complete reduction of xerosis in 17 (81%) patients. Symptoms of dry skin reappeared in four patients 14 days after the end of therapy, so at follow-up visit 13 (61.9%) patients still had smooth skin.

Xerosis scores were significantly reduced throughout the study period (Tables 2 and 3, Fig. 4). A marked reduction (statistically significant) was observed between baseline and day 7 as well as between day 7 and day 14 of the evaluation. Upon completion of the trial, the scores for dry skin increased, however, the difference between day 21 (end of therapy) and follow-up visit did not reach statistical significance. At follow-up visit xerosis remained significantly less intensive compared to the beginning of the study.

The test product was very well tolerated by all patients (100%). Neither functional nor physical side effects were observed.

At the end of the study cream application, 11 (52.4%) patients found the final result of the treatment to be satisfactory, eight (38.1%) patients considered it very satisfactory, and only two (9.5%) patients stated the therapeutic result to be only poorly satisfactory (Fig. 5).

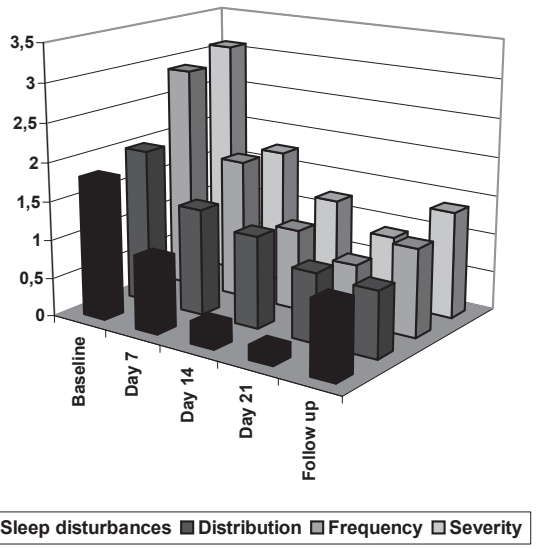

Figure 3. Elements of pruritus evaluation (questionnaire method) during therapy.

Table 3. Statistical analysis of pruritus and xerosis scores during treatment

		(1) vs. (2)	(2) vs. (3)	(3) vs. (4)	(4) vs. (5)	(1) vs. (4)	(1) vs. (5)
Pruritus	VAS	p=0.0001	p=0.006	p<0.05	p=0.025	p<0.0001	p=0.0001
	Questionnaire	p=0.006	p=0.044	p=0.052	NS	p<0.0001	p=0.0002
	Distribution	p=0.011	NS	NS	NS	p=0.0005	p=0.0007
	Frequency	p=0.002	p=0.056	NS	NS	p=0.0007	p=0.0009
	Severity	p=0.0007	NS	p<0.05	NS	p=0.001	p=0.002
	Sleep disturbances	NS	NS	NS	p=0.04	p=0.01	NS
Xerosis		p=0.0004	p=0.03	NS	NS	P=0.0001	p=0.0007

NS = nonsignificant

DISCUSSION

To the best of our knowledge, this is the first study evaluating topical application of a preparation containing endocannabinoids in the treatment of uremic pruritus. In an open study, we demonstrated that the preparation with structured natural lipids (DMS®) and endocannabinoids could be helpful in controlling itching and xerosis in patients on maintenance hemodialysis. However, as the pathogenesis of uremic pruritus is not fully known, the exact mechanism of antipruritic action of the tested cream could only be hypothesized.

One of the most important functions of healthy skin is to function as a barrier between the environment and the body. This function can only be fulfilled by intactness of its lipid permeability barrier, a unique stack of bilayers assembled in the epidermis from a mixture of biomolecules (5). In hemodialysis patients, the skin is dry because the

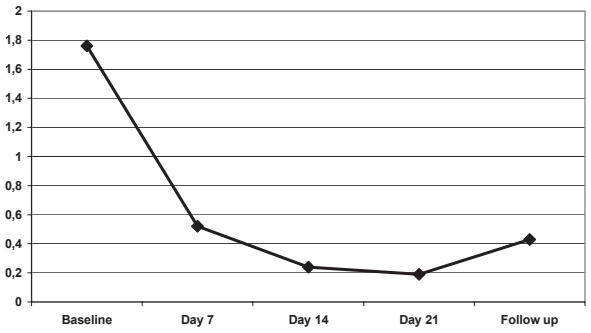

Figure 4. Xerosis scores during therapy.

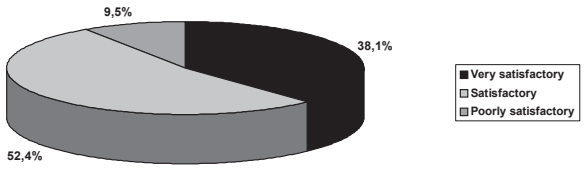

Figure 5. Patient assessment of therapy efficacy (pruritus reduction).

lipid barrier is often damaged (3,4). This can result in intense itching in such patients. Some studies even showed a correlation between uremic pruritus and intensity of xerosis (1). Therefore, it is reasonable to use emollients in this group of individuals, which was clearly mentioned in the recent guidelines for controlling itching in systemic diseases (6). The majority of the skin-care products contain emulsifiers to disperse lipids in the formulation. These emulsifiers could damage or even destroy the continuous-bilayer structure in the skin. The preparation evaluated in the present study does not contain any emulsifiers, as it contains a unique structure of active lipids similar to the lipids of stratum corneum, which are dispersed in the concentrate in a lamellar structure similar to the physiological structure of the lipids of the stratum corneum. Moreover, the active lipids are combined to classic ingredients with moisturizing properties. Such a formula could be responsible for the very good effect in the treatment of xerosis, as also demonstrated in other clinical studies (7,8).

Although the antipruritic action of the preparation evaluated could be related to the moisturizing effect of the tested cream, it is very likely that the pruritus reduction with the test product application was not only the result of dry skin improvement. At the beginning of the trial, there was no significant correlation between the intensity of xerosis and severity of pruritus in the study patients. We do believe that the final result could have been influenced by the additional ingredients of endocannabinoids. The endocannabinoids (N-acetylethanolamine – AEA and N-palmitoylethanolamine – PEA), which are normally found in the lipid fraction of rat brain, liver, skeletal muscle, paw skin and testis (9), could interact with the peripheral cannabinoid receptors. It has been shown that human keratinocytes partake in the peripheral endocannabinoid system (10). Rukwied *et al.* (11) proved that cannabinoid receptor agonists significantly reduced histamine-induced itch and vasodilatation by applying them topically before the administration of histamine. In addition, coadministration of selective cannabinoid 1 receptor agonists with histamine markedly reduced the axon reflex flare response (11). Moreover, PEA has been demonstrated to down-modulate mast cell degranulation induced either by neurogenic (substance P) or immune-mediated stimuli, both in vitro and in vivo (12,13). PEA also exerts a potent inhibitory effect on cytokines (interleukins 4, 6, 8) release from macrophages and peripheral blood mononuclear cells (14), and decreases the levels of tumor necrosis factor α (TNF-α) during inflammation (15). It also inhibits nitric oxide macrophage production induced by lipopolysaccharide (16). Additionally, in the rat paw formalin-induced pain test PEA was able to activate an analgesic response (17). The results of clinical and histologic evaluation of PEA in cats with eosinophilic granuloma demonstrated that after one month of treatment, 64% of all animals given PEA showed improvement of pruritus, erythema and alopecia, and 67% revealed improvement of the extent and severity of the lesion (18). Moreover, treatment for 30 days with PEA significantly increased densitometric values of cutaneous mast cells, suggesting that PEA is able to effectively decrease mast cell degranulation and increase intracellular concentration of mast cell granules. Finally, in cats with eosinophilic plaque, the clinical improvement directly correlated with the increase in mast cell densitometry and this correlation was highly significant despite the small number of cases (18). All these findings could indicate that endocannabinoids may bring relief in uremic pruritus *per se*, as several phenomena mentioned above (effect on mast cells, histamine and cytokines) could play a role in the pathogenesis of uremic pruritus. The anti-inflammatory and anti-nociceptive properties of endocannabinoids may possibly be responsible for their antipruritic effect (9,19). Mast cells could also be regarded

as a target point of endocannabinods in relieving uremic pruritus, as several studies showed an increased mast cell density in patients suffering from uremic pruritus (20-23). Moreover, in these patients mast cells were mainly degranulated and dispersed throughout the skin. Additionally, tryptase and chymase discrepancies were found in the skin of hemodialysis patients with uremic itch (20,21).

It is important to note that the majority of our patients considered the final effect of the applied treatment satisfactory or very satisfactory in pruritus reduction.

In conclusion, this preliminary clinical study suggested that the synergistic effect of the natural ingredients (essential fatty acids embedded into the Derma-Membrane-Structure® and the composition of endocannabinoids) may help restore typical skin reactions such as pruritus and xerosis in hemodialysis patients. However, additional controlled studies are needed to confirm its usefulness in uremic itch and uremic xerosis.

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References

1. Szepietowski JC, Sikora M, Kusztal M, Salomon J, Magott M, Szepietowski T. Uraemic pruritus: a clinical study of maintenance haemodialysis patients. J Dermatol 2002;29:621-7.
2. Zucker I, Yosipovitch G, David M, Gafter U, Boner G. Prevalence and characterization of uremic pruritus in patients undergoing hemodialysis: uremic pruritus is still a major problem for patients with end-stage renal disease. J Am Acad Dermatol 2003;49:842-6.
3. Urbonas A, Schwartz RA, Szepietowski JC. Uremic pruritus – an update. Am J Nephrol 2001;21:343-50.
4. Szepietowski JC, Schwartz RA. Uremic pruritus. Int J Dermatol 1998;37:247-53.
5. Vacata V, Grtchen-Ohlinschläger B, Ghyczy M. Topical formulations conforming to the structure of the skin. Cosmetics Toiletries 2001;116:67-74.
6. Twycross R, Greaves MW, Handwerker H, Jones EA, Libretto SE, Szepietowski JC, *et al*. Itch: scratching more than the surface. Q J Med 2003;96:7-26.
7. Brüning H, Knaussmann HG, Rüther TH, Ude P. Physiogel® cream – a new base therapy for patients with neurodermatitis. Hautnah Schweiz 2002;1:35-8.
8. Szepietowski J, Salomon J. Physiogel® cream: therapeutic effects of the treatment of dry skin. Dermatol Estet 2003;5:195-9.
9. Lambert DM, Vandevoorde S, Jonsson KO, Fowler CJ. The palmitoylethanolamide family: a new class of anti-inflammatory agents? Curr Med Chem 2002;9:663-74.
10. Maccarrone M, Di Rienzo M, Battista N, Gasperi V, Rossi A, Finazzi-Agro A. The endocannabinoid system in human keratinocytes. Evidence that anandamide inhibits epidermal differentiation through CB1 receptor-dependent inhibition of protein kinase C, activating protein-1 and transglutamidase. J Biol Chem 2003;278:33896-903.
11. Rukwied R, Dvorak M, Watkinson A, McGlone F. Putative role of cannabinoids in experimentally induced itch and inflammation in human skin. In: Yosipovitch G, Greaves MW, Fleischer AB Jr, McGlone F, editors. Itch: basic mechanisms and therapy. New York: Marcel Dekker Inc; 2004. p. 115-30.
12. Facci L, Dal Toso R, Romanello S, Buriani A, Skaper SD, Leon A. Mast cells express a peripheral cannabinoid receptor with differential sensivity to anandamide and palmitoylethanolamide. Proc Natl Acad Sci USA 1995;92:3376-80.
13. Mazzari S, Canela R, Petrelli L Marcolongo G, Leon A. N-(2-hydroxyethyl) hexadecanamide is orally active in reducing edema formation and inflammatory hyperalgesia by down-modulating mast cell activation. Eur J Pharmacol 1996;300:227-36.
14. Berdyschev EV, Boichot E, Corbel M, Germain N, Lagente V. Influence of fatty acid ethanolamides and delta 9-tetrahydrocannabinol on cytokine and arachidonate release by mononuclear cells. Eur J Pharmacol 1997;330:231-40.
15. Berdyshev EV, Boichot E, Corbel M, Germain N, Lagente V. Effects of cannabinoid receptor ligands on LPS-induced pulmonary inflammation in mice. Life Sci 1998;63:PL 125-29.
16. Costa B, Conti S, Giagnoni G, Colleoni M. Therapeutic effect of the endogenous acid amide, palmitoylethanolamide, in rat acute inflammation: inhibition of nitric oxide and cyclo-oxygenase systems. Br J Pharmacol 2002;137:413-20.
17. Jaggar SI, Hasnie FS, Sellaturay S, Rice AS. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB2 receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. Pain 1998;76:189-99.

18. Scarampella F, Abramo F, Noli C. Clinical and histological evaluation of an analogue of palmitoylethanolamide, PLR 120 (comicronized Palmidrol INN) in cats with eosinophilic granuloma and eosinophilic plaque: a pilot study. Vet Dermatol 2001;12:29-39.
19. Conti S, Costa B, Colleoni M, Parolaro D, Giagnoni G. Antiinflammatory action of endocannabinoid palmitoylethanolamide and the synthetic cannabinoid nabilone in a model of acute inflammation in the rat. Br J Pharmacol 2002;135:181-7.
20. Szepietowski J, Thepen T, van Vloten WA, Szepietowski T, Bihari IC. Pruritus and mast cell proliferation in the skin of haemodialysis patients. Inflamm Res 1995;44 (Suppl 1):S84-S85.
21. Szepietowski J. Selected elements of the pathogenesis of pruritus in haemodialysis patients: the own study. Med Sci Monit 1996;2:343-7.
22. Matsumoto M, Ichimaru K, Horie A. Pruritus and mast cell proliferation of the skin in end stage renal failure. Clin Nephrol 1985;23:285-8.
23. Leong SO, Tan CC, Lye WC, Lee EJ, Chan HL. Dermal mast cell density and pruritus in the end stage renal failure. Ann Acad Med Singapore 1994;23:327-9.

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