



Management of refractory pruritus with difelikefalin in a patient on incremental hemodialysis one day a week: Is it safe and effective?

Manejo del prurito refractario con difelikefalina en un paciente en hemodiálisis incremental de un día a la semana. ¿Es seguro y eficaz?

Dear Editor,

Uraemic pruritus (UP) is one of the symptoms with more effects on the quality of life of the haemodialysis (HD) population. Despite its high prevalence (30–70%), it is not treated adequately.¹ Difelikefalin (DFK) is a peripheral kappa-opioid receptor agonist recently approved for the treatment of UP.² However, experience of DFK in patients on incremental haemodialysis (iHD) is limited.

We present the case of a 62-year-old woman with a right nephrectomy due to severe hydronephrosis secondary to lithiasis, arterial hypertension and type 2 diabetes mellitus. HD was started due to poor blood pressure control, hyperkalaemia, uraemic symptoms and generalised pruritus, with one weekly session of 240 min and asymmetric cellulose triacetate dialyser-1.9 m² (ATA[®]). At the beginning of iHD, there was a clearance of creatinine (ClCr) and urea (KrU) measured by 24-h urine and residual diuresis of 16; 4.70 ml/min/1.73 m² and 1900 ml respectively.

Due to the persistence of pruritus, dermatological, haematological, hepatic/biliary, neurological, psychiatric and pharmacological causes were ruled out. The patient maintained standard Kt/V adjusted to body surface area greater than 2.3 weekly volumes, high convective volume and residual diuresis with KrU > 4 ml/min. Therefore, it was considered justified not to increase the dialysis dose (Table 1). Initial treatment with moisturisers, dermal emollients, gabapentin and mirtazapine were unsuccessful. The severity of pruritus and the impact on quality of life were evaluated using the WIN-RS and SADS³ questionnaires, presenting 8 points and a moderate degree, respectively. Given the persistence of symptoms, IV DFK was requested (0.5 µg/kg/pos-HD weekly) through the Early Access Program. After 12 weeks of treatment, pruritus was reduced to 4 points and a mild degree on the WIN-RS and SADS scales, respectively (Table 1). The patient did not have adverse effects with this drug during follow-up.

The management of UP continues to be complex due to its multifactorial origin. After ruling out secondary causes, different topical and systemic pharmacological treatments

were proposed, with gabapentin being the only drug with a proven effect on UP.¹ Furthermore, it has been classically associated with low-flow dialysis and blood levels. Kt/V < 1.51.⁴ There was a hypothesis that those patients who maintained residual renal function on peritoneal dialysis were associated with a lower incidence of UP due to the elimination of larger molecules,⁵ but recent studies have not found such a relationship.⁶ In addition, within HD techniques, high-flow HD, online haemodiafiltration and adsorptive HD are associated with improvement in PU symptoms,⁷ as these techniques are considered to improve the purification of uraemic toxins and the inflammatory state. However, to date, none of these dialysis treatments have been shown to be effective in preventing UP. Only kidney transplantation significantly improves the symptoms of UP.⁷

In a recent clinical trial, 378 HD patients with moderate-severe pruritus were randomised 1:1 to receive DFK and placebo, 3 times a week post-HD, for 12 weeks. DFK demonstrated rapid efficacy with a significant reduction in pruritus by at least 3 points on the WIN-RS itch scale compared to placebo (51.9% vs. 30.9%), providing an improvement in quality of life.⁸ However, studies conducted in the HD population only include patients with the conventional 3-day-a-week regimen, without including iHD patients.

For the first time, our case describes the efficacy and safety of DFK in the management of pruritus in a patient on iHD with one session per week. In our centre, in incident patients, the frequency of HD doses is adjusted based on KrU, following the criteria collected in the DIPPI⁹ study and the recommendations of the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) of 2015.¹⁰ During follow-up, our patient maintained unchanged diuresis, CrCl and KrU, with correct HD efficacy values, without the need to increase the frequency of the dialysis dose. The new document from the Spanish Society of Nephrology (SEN) on the management of pruritus in HD¹¹ recommends the prescription of DFK for refractory cases.

According to our experience, in patients with adequate renal and dialytic clearance who present refractory pruritus, the use of DFK is useful and safe, and avoids increasing the

Table 1 – Analytical evolutionary control, haemodialysis parameters and pruritus assessment scales.

	Start of haemodialysis	Baseline	Week 4	Week 8	Week 12
Hb (g/dl)	11.5	12	11.5	11.2	11.3
Na ⁺ (mmol/l)	139	139	136	137	140
K ⁺ (mmol/l)	5.9	5.2	4.9	4.8	4.7
Uric acid (mg/dl)	8.8	7.8	7.4	7.2	6.8
Serum albumin (mg/dl)	2.8	3.2	3.2	3.3	3.3
Serum glucose (mg/dl)	148	154	154	150	157
HbA1c (%)	6.5	6.2	N/A	N/A	6.0
Weight (kg)	70.5	69.5	68.4	67	67
Phosphorus (mg/dl)	5.7	4.9	4.5	4.5	4.7
Calcium (mg/dl)	9	8.9	8.9	8.7	8.8
PTH (pg/ml)	189	180	210	212	288
25-Hydroxy-vitamin D (ng/ml)	17	14.5	20.5	26	28
Direct bilirubin (mg/dl)	0.8	0.9	1	0.9	0.8
WI-NRS	8	8	7	6	4
SADS	Moderate	Moderate	Moderate	Mild	Mild
Serum creatinine (mg/dl)	4.5	4.35	4.21	4.06	4.5
Serum urea (mg/dl)	121	128	123	129	126
CKD-EPI (ml/min)	10	11	11	12	10
Residual diuresis (ml/24 h)	1900	1800	2200	2500	2200
KrU (ml/min)	4.7	6.2	6.3	6.5	6.3
ClCr (ml/min/1.73 m ²)	16	16	17	20	19
IFG (ml/min/1.73 m ²)	10.3	10.3	10.75	12.75	11.75
Bicarbonate (mmol/l)	15	18.8	20.3	24.3	20
ACR (mg/g)	3300	3300	3100	2800	2300
VB (l)	N/A	80	82	85	86
Vinf-OL-HDF (l)	N/A	24	26.4	26	25.3
Kt/v (L)	N/A	1.45	1.55	1.55	1.55
BSA-normalised std Kt/V (l)	N/A	5.24%	5.49	5.87	5.48.
EKRU Casino (ml/min)	N/A	18.1	18.6	19.4	18
KT (l)	N/A	53	56.7	54	56
IDWG (kg)	N/A	1	1.2	0.9	0.8

ACR: albumin/creatinine ratio; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CrCl: 24-h urinary Cr clearance; IDWG: interdialytic weight gain; Hb: haemoglobin; Hb1Ac: glycated haemoglobin; HD: haemodialysis; GFR: glomerular filtration rate; K⁺: plasma potassium; KrU: residual renal urea clearance; KT: efficacy of dialysis treatment; N/A: not assigned; na⁺: plasma sodium; PTH: parathormone; SADS: Patient Assessed Severity of Illness Scale; BSA-normalised std Kt/V: standard Kt/V normalised to body surface area; Vinf-OL-HDF: infusion volume in online hemodiafiltration; VB: dialysed blood volume; WI-NRS: worst itch numeric rating scale.

dialysis dose. This allows us to preserve the quality of life of patients and reduce the cost associated with a greater number of weekly sessions.¹²

Ethical responsibilities

The study complied with the principles set out in the Declaration of Helsinki. The authors declare they received the informed consent of the subject studied, and respect the patient's right to privacy. No experiments were performed on humans or animals for this study.

Conflicts of interest

The author has no conflicts of interest or financial support to declare.

REFERENCES

- Santos-Alonso C, Maldonado Martín M, Sánchez Villanueva R, Álvarez García L, Vaca Gallardo MA, Bajo Rubio MA, et al. Pruritus in dialysis patients. Review and new perspectives. *Nefrologia* [Internet]. 2022 Jan 1;42:15–21 [Accessed 16 June 2023]; Available from: <https://pubmed.ncbi.nlm.nih.gov/36153894/>
- Kapruvia | European Medicines Agency [Internet]. [Accessed 16 June 2023]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/kapruvia>.
- Mathur VS, Lindberg J, Germain M, Block G, Tumlin J, Smith M, et al. A longi-tudinal study of uremic pruritus in hemodialysis patients. *Clin J Am Soc Nephrol* [Internet]. 2010 Aug 1;5:1410–9 [Accessed 16 June 2023]; Available from: <https://pubmed.ncbi.nlm.nih.gov/20558560/>
- Ko MJ, Wu HY, Chen HY, Chiu YL, Hsu SP, Pai MF, et al. Uremic Pruritus, Dialysis Adequacy, and Metabolic Profiles in Hemodialysis Patients: A Prospec-tive 5-Year Cohort Study. *PLoS One* [Internet]. 2013;8 [Accessed 16 June 2023]; Available from: <https://pubmed.ncbi.nlm.nih.gov/26945400/>
- Wu HY, Sen Peng Y, Chen HY, Tsai WC, Yang JY, Hsu SP, et al. A Compari-son of Uremic Pruritus in Patients Receiving Peritoneal Dialysis and Hemodialy-sis. *Medicine* [Internet]. 2016;95(9) [Accessed 16 June 2023]; Available from: <https://pubmed.ncbi.nlm.nih.gov/26945400/>

6. Min JW, Kim SH, Kim YO, Jin DC, Song HC, Choi EJ, et al. Comparison of uremic pruritus between patients undergoing hemodialysis and peritoneal dialysis. *Kidney Res Clin Pract* [Internet]. 2016;35:107 [Accessed 16 June 2023]; Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4919557/pdf/main.pdf>
7. Molina P, Ojeda R, Blanco A, Alcalde G, Prieto-Velasco M, Aresté N, et al. Etiopatogenia del prurito asociado a la enfermedad renal crónica: recomponiendo las piezas del puzle. *Nefrología* [Internet]. 2023;43:48-62 [Accessed 16 June 2023]; Available from: <https://www.revistanefrologia.com/es-etipatogenia-del-prurito-asociado-enfermedad-articulo-S0211699522001163>
8. Fishbane S, Jamal A, Munera C, Wen W, Menzaghi F. A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus. *N Engl J Med* [Internet]. 2020;382:222-32 [Accessed 16 June 2023]; Available from: <https://pubmed.ncbi.nlm.nih.gov/31702883/>
9. Suárez MA, García-Cabrera E, Gascón A, López F, Torregrosa E, García GE, et al. Justificación y diseño de DiPPI: un ensayo controlado aleatorizado para evaluar la seguridad y la efectividad de la hemodiálisis progresiva en pacientes incidentes. *Nefrología*. 2018;38:630-8.
10. Rocco M, Daugirdas JT, Depner TA, Inrig J, Mehrotra R, Rocco MV, et al. KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 Update. *American Journal of Kidney Diseases* [Internet]. 2015;66:884-930 [Accessed 08 February 2021]; Available from: <http://www.ajkd.org/article/S0272638615010197/fulltext>
11. Buades JM, Figueras-Nart I, Goicoechea M, Sánchez Villanueva RJ, Serra-Baldrich E. Documento de información y consenso para el manejo diagnóstico y terapéutico del prurito asociado a la enfermedad renal crónica en pacientes en hemodiálisis en España. *Nefrología* [Internet]. 2023 [Accessed 16 June 2023]; Available from: <https://www.revistanefrologia.com/es-pdf-S021169952300067X>
12. Caton E, Sharma S, Vilar E, Farrington K. Impact of incremental initiation of haemodialysis on mortality: a systematic review and meta-analysis. *Nephrol Dial Transplant* [Internet]. 2023 Feb 1;38:435-46 [Accessed 16 June 2023]; Available from: <https://pubmed.ncbi.nlm.nih.gov/36130107/>

José C. de la Flor^{a,*}, Leonardo Cruzado^b, Javier Deira^c, Francisco Valga^d, Beatriz Sualdea^a, Rocio Zamora^e, Miguel Rodeles^a

^a Servicio de Nefrología, Hospital central de la defensa Gómez Ulla, Madrid, Spain

^b Servicio de Nefrología, Hospital General de Elche, Alicante, Spain

^c Servicio de Nefrología, Hospital San Pedro de Alcántara, Cáceres, Spain

^d Servicio de Nefrología, Hospital Universitario Dr. Negrín, Las Palmas de Gran Canarias, Spain

^e Servicio de Nefrología, Hospital Universitario General Villalba, Madrid, Spain

*Corresponding author.

E-mail address: jflomer@mde.es (J.C. de la Flor).

2013-2514/© 2023 Sociedad Española de Nefrología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). <https://doi.org/10.1016/j.nefro.2024.06.005>

Treatments and diets associated with resistant arterial hypertension and their influence on the efficacy of spironolactone

Tratamientos y dietas asociadas a la hipertensión arterial resistente y su influencia en la eficacia de la espironolactona



Dear Editor,

The article published by Galceran et al. entitled: “Evolution of Hypertension mediated organ damage in patients with resistant hypertension patients after adding spironolactone”¹ provides an advance in the knowledge of the treatment of resistant arterial hypertension (RHTN), since it finds spironolactone as an efficient treatment. However, we would like to highlight some observations regarding the study.

The Materials and Methods section does not specify whether the study participants received additional treatment for any comorbidity or arterial hypertension itself. It is known that for the management of RHTN, the combination of angiotensin-converting enzyme inhibitors such as enalapril, a calcium antagonist such as nifedipine, and a thiazide diuretic such as chlorthalidone produces a reduction of blood pressure.^{2,3} In addition, it is known that patients with hypertension receive low-salt diets and are forbidden to consume any type of alcoholic beverage, based on the knowledge

DOI of original article:

<https://doi.org/10.1016/j.nefro.2023.08.003>.