

# ON101 Cream Increases the Wound Healing Rate in Diabetic Patients with Uremia—Cases Report

Yu-Hsiu Yen<sup>1,2</sup>, Chi-Ming Pu<sup>1,3\*</sup>

<sup>1</sup>Division of Plastic Surgery, Department of Surgery, Cathay General Hospital, Taipei City

<sup>2</sup>School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei

<sup>3</sup>School of Medicine, College of Life Science, National Tsing Hua University, Hsinchu

Email: \*pkman9335@msn.com

**How to cite this paper:** Yen, Y.-H. and Pu, C.-M. (2024) ON101 Cream Increases the Wound Healing Rate in Diabetic Patients with Uremia—Cases Report. *Case Reports in Clinical Medicine*, 13, 178-186.

<https://doi.org/10.4236/crcm.2024.135020>

**Received:** April 12, 2024

**Accepted:** May 25, 2024

**Published:** May 28, 2024

Copyright © 2024 by author(s) and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

## Abstract

Diabetic patients who underwent long-term dialysis may increase the prevalence of foot ulceration. In addition, diabetic foot ulcer (DFUs) patients with end-stage renal disease (ESRD) do not heal well, and the amputation rate is 6.5 - 10 times higher compared to the non-nephropathic diabetic population. Thus, a suitable therapeutic agent was needed. ON101 is a topical cream that promotes diabetic wound healing through a unique macrophage-regulating ability. In this case series, we included 5 diabetes patients (mean age  $54.6 \pm 8.7$  years, 4 mal) with ESRD (mean eGFR  $7.4 \pm 3.35$  mL/min/1.73m<sup>2</sup>) and had experienced dialysis for at least 4.5 years. These patients also have UT (University of Texas) grade 2A DFUs that have existed for at least 1.5 months (mean ulcer duration  $8.3 \pm 8.97$  months). These subjects were applied ON101 twice daily for up to 20 weeks, and wound size was recorded during treatment. Among these subjects, three ulcers (patient No. 1, 2, and 3) completely healed within 10 weeks upon ON101 application, and one ulcer was 99% reduced at 20<sup>th</sup> weeks (patient No. 4). Only one ulcer didn't show an obvious response that may due to poor compliance in wound care and glucose control. In summary, the overall healing rate was 60%, suggesting ON101 performed equivalence healing efficacy in dialysis patients compared with those who did not have dialysis.

## Keywords

Diabetic Foot Ulcer (DFU), Uremia, Dialysis, Wound Healing

## 1. Introduction

Diabetes is one of the most common diseases worldwide, estimated to affect 693

million adults by 2045, according to the report of the International Diabetes Federation (IDF) [1]. Vascular complications, including cardiovascular disease (CVD), chronic kidney disease (CKD), diabetic retinopathy, and neuropathy, are the leading cause of morbidity and mortality in diabetic patients [2]. CKD as well as the leading cause of end-stage renal disease (ESRD), suggested diabetic patients were at a higher risk to lose renal functions and need undergo lifelong dialysis or even renal transplantation [3] [4].

Diabetic foot ulcer (DFU) affects up to 34% of diabetes patients, causing enormous economic burden and reducing life quality [5]. The International Working Group on the Diabetic Foot (IWGDF) has proposed that diabetic patients with ESRD should be classified as category 3 in podiatric risk [6], suggesting that impaired renal function is tightly associated with ulcer management strategies. Studies revealed that dialysis is a critical risk factor for the prevalence of ulceration in diabetes patients [7] [8] [9]. In addition, diabetic patients who undergo dialysis treatment have disproportionately higher rates of amputation caused by poor healing rate [10] [11] [12]. Furthermore, a retrospective study demonstrated that reduced eGFR level, which means regression of kidney function, in patients with DFU was associated with poor prognoses of both the limbs and mortality [13]. These observations indicate that impaired renal function and dialysis treatment would prolong diabetic foot ulcer healing. Hence, the improvement of the healing rate of DFU patients whose renal function was impaired and who underwent dialysis was an emergent medical need.

ON101 topical cream has effectively promoted wound healing in diabetic patients by modulating the activity of M1 and M2 macrophages [14] [15]. Current research revealed long-term peritoneal dialysis results in acute and chronic inflammation, with elevated relative inflammatory cytokines [16]. A hypothesis was made that ON101 may overcome the chronic inflammation caused by dialysis and efficiently promote wound healing. Here, we report five dialysis patients who receive ON101 as a therapeutic option to manage their DFUs in Taiwan region. The results indicate that ON101 maintained good healing efficacy in dialysis DFUs.

## 2. Case Series

### 2.1. Case 1

A 64-year-old male patient with hypertension, type 2 DM, and uremia under regular hemodialysis for more than 6 years. He has a high BMI of 34.9 and has smoked a pack of cigarettes every day for more than 50 years. He visited the plastic surgery outpatient department (OPD) of Cathay General Hospital (CGH) due to a chronic unhealed wound with pus discharge at the right lateral malleolar area for 2 weeks. He suffered from a right ankle fracture post ORIF for 10 years, and multiple implanted nails were found in the X-ray. The duplex scan showed 50% stenosis of the right anterior tibia artery. After multiple debridements, negative pressure wound therapy and parenteral antibiotics treatment,

the wound is getting better, and the patient is discharged from the hospital, followed by OPD management. However, 2 months after he was discharged, the wound size didn't decrease due to persistent inflammation with over-granulation tissue, even though we used other kinds of artificial dressings to treat the wound. We used a new macrophage-modulating drug, ON101 (Oneness Biotech Co, Ltd., Taiwan region), for wound treatment. The wound size was 8.96 cm<sup>2</sup> when he started to use the ON101 (Figure 1(a)). We applied topically with gauze twice daily, the wound quickly down-grade from 2A to 1A after 2 weeks of treatment (Figure 1(b)) and completely healed 8 weeks after ON101 application (Figure 1(c), Table 1).

## 2.2. Case 2

A 60-year-old male patient is a victim of parkinsonism and uremia under regular hemodialysis for more than 10 years. He also suffered from hyperlipidemia, CAD and congestive heart disease. He came to plastic surgery OPD of CGH due to right foot pain, and right 5<sup>th</sup> toe gangrene noted for several weeks. Right 5<sup>th</sup> toe amputation was performed, but he encountered poor wound healing after surgery. He was admitted for further wound management. Surgical debridement was performed, and an artificial dermis was applied to the wound. But the

**Table 1.** Demography information of five subjects.

Subjects	No. 1	No. 2	No. 3	No. 4	No. 5
<b>Demography</b>					
Age (year)	64	60	55	40	53
Sex	M	M	F	M	M
BMI	34.9	20.7	25.8	34.3	24.2
DM Duration	>30 y	>20 y	>8 y	>10 y	>20 y
HbA1c (%)	8.0	4.8	7.4	5.7	5.5
<b>Ulcer condition</b>					
Target ulcer duration (months)	1.5 m	6 m	6 m	4 m	24 m
Ulcer Size (cm <sup>2</sup> )	8.96	7.27	5.74	7.47	8.80
UT grade	2A	2A	2A	2A	2A
<b>Renal factors</b>					
Dialysis type	HD	HD	HD	HD	PD
Dialysis Duration (years)	>6 y	>10 y	8 y	>10 y	>4.5 y
Creatinine (mg/dL)	8.51	4.55	6.72	11.30	9.40
eGFR (mL/min/1.73m <sup>2</sup> )	6.4	13.3	6.4	5.0	5.9
<b>After treatment</b>					
Healing condition	100% within 8 weeks	100% within 10 weeks	100% within 10 weeks	99% within 20 weeks	0% within 20 weeks

BMI, Body Mass Index; DM, Diabetes Mellitus; UT, University of Texas; eGFR, estimated Glomerular filtration rate.



**Figure 1.** Patient No. 1 with target ulcer on right ankle. (a) Before treatment; (b) 2 weeks of ON101 treatment; (c) 8 weeks after ON101 treatment.

wound didn't show improvement. The duplex scan showed a right posterior tibia artery occlusion. The patient refused further surgical reconstruction, including percutaneous transluminal angioplasty. So, we suggested the patient receive ON101 treatment, which was applied topically with gauze twice daily. The wound size was 7.27 cm<sup>2</sup> when he started to use ON101 (**Figure 2(a)**) and down-grade from 2A to 1A within 2 weeks with 48% wound size reduction (**Figure 2(b)**). The wound got 87% size reduction 6 weeks after ON101 application (**Figure 2(c)**) and healed completely at 10<sup>th</sup> weeks of ON101 usage (**Figure 2(d)**). The target ulcer didn't show recurrence for 16 months (**Table 1**).

### 2.3. Case 3

A 55-year-old female patient has been a victim of CVA (Cardiovascular accident) and hemiparalysis for several years. She can only ambulate by wheelchair and lay in bed most of the time. She was also diagnosed with type 2 DM and uremia under regular hemodialysis for 8 years. This time, she suffered from a plantar ulcer on her left heel for about six months. The wound is located in a pressure region with some necrotic tissue. The Duplex scan showed no remarkable change in the left lower leg arteries. We debrided the necrotic tissue at clinics and used sulfadiazine silver cream to treat the wound for 3 weeks, but the wound didn't improve. Then, we used AquaCel Ag to treat the wound for another 3 weeks, and the wound didn't show any improvement. The wound looked persistent inflammation stage and showed unhealthy granulation tissue, and the size was 5.74 cm<sup>2</sup> (**Figure 3(a)**). So, ON101 was instead applied topically with gauze twice daily, and the wound size reduced to 2.01 cm<sup>2</sup> at 6 weeks of ON101 application (**Figure 3(b)**) and healed completely after 10 weeks (**Figure 3(c)**) and didn't show recurrence for 6 months (**Table 1**).



**Figure 2.** Patient No. 2 with target ulcer on right 5<sup>th</sup> toe. (a) Before treatment; (b) 2 weeks of ON101 treatment; (c) 6 weeks after ON101 treatment; (d) 10 weeks after ON101 treatment.



**Figure 3.** Patient No. 3 with target ulcer on left heel. (a) Before treatment; (b) 6 weeks of ON101 treatment; (c) 10 weeks after ON101 treatment.

#### 2.4. Case 4

A 40-year-old male patient diagnosed with type 2 DM, uremia, and under regular hemodialysis for more than 10 years. He has a high BMI of 34.3 and has smoked less than a pack of cigarettes every day for more than 20 years. The wound on the side of his left foot had been present for about four months. The Duplex scan showed the suspected hematoma near left SFA proximal portion. We debrided the necrotic tissue at clinics and used AquaCel Ag to treat the wound, but the wound didn't improve. So, we suggested that the patient receive ON101 treatment, which is applied topically with gauze twice daily. The wound size was 7.47 cm<sup>2</sup> when he started to use the ON101. The wound was reduced by

99% and almost completely healed in 20 weeks after using ON101 (Table 1).

### 2.5. Case 5

A 53-year-old male patient diagnosed with type 2 DM, uremia, and under regular peritoneal dialysis (PD) for more than 4.5 years. He also suffered from hyperlipidemia, chronic ischemic heart disease, and peripheral vascular disease. The wound on the right heel, which is located in a pressure region, had been present for about two years. The Duplex scan showed diffuse atherosclerosis involving bilateral lower limb arteries. Surgical debridement and split-thickness graft were applied to the wound to promote wound healing. After the surgery, the wound was treated with Aquacel Extra hydrofiber for 4 weeks, but the wound didn't improve. So, we suggested that the patient receive ON101 treatment, which was applied topically with gauze twice daily. The wound size was 8.80 cm<sup>2</sup> when he started to use the ON101. The wound has not improved after using ON101 for 20 weeks (Table 1).

## 3. Discussion

DM patients encountered multiple complications and impaired wound healing due to systemic inflammation. The vascular access-related infectious complications and dialysis solutions during dialysis exaggerate local and systemic inflammation, which even increases the mortality rate [17] [18]. In such circumstances, wounds in diabetic patients are more challenging to heal, leading to an increased likelihood of amputation and a heavier burden on daily life. We report five DFU patients who have been on dialysis for at least 4.5 years, and the average ulcer sizes were 7.65 cm<sup>2</sup> before applying ON101. Three ulcers healed within 10 weeks when daily ON101 applications and one ulcer was reduced for 99% at 20 weeks of the treatment period. The complete healing rate is 60% within 10 weeks in these five patients, suggesting ON101 displayed consistent healing efficacy in dialysis cohorts compared to those without [15]. Such a result further confirmed the macrophage regulative ability of ON101 could target DFU patients who are undergoing dialysis.

Among the five cases, patient No. 5 is the only one who performed PD and the ulcer did not improve after ON101 was used. Although patient No. 5 didn't display nutritional insufficiency, peritoneal dialysis was known to lose more protein and nutrition than hemodialysis [19]. Previous studies demonstrated excessively high dialysate glucose load caused by long-term PD may exacerbate the glycemia conditions in DM patients [20]. Indeed, the HbA1c level of patient No. 5 was elevated during the treatment period (HbA1c from 5.5% to 9.3%). In addition to poor glycemic control, this patient has plantar ulcers at both heels, which could not be off-loading properly, and the target ulcer has existed for 24 months, suggesting that there may be other extrinsic factors affecting the wound healing of patient 5.

Except patient No. 5, the remaining four subjects demonstrated significant

reduction in ulcer size under ON101 treatment regardless of the low eGFR and long-term dialysis history (**Table 1**). Conclusively, ON101 exhibits a unique mechanism by rebalancing the population of M1 and M2 macrophages and, in turn, reshaping the wound microenvironments to facilitate hard-to-heal ulcers to healing. Therefore, it suggests that ON101 would be an ideal treatment option for patients who have DFUs and are undergoing dialysis.

## Acknowledgements

We would like to thank study nurse Jia-Ying Lin for their care of the patients. We would like to thank Onenessbio Co., Ltd. for kindly provide ON101. We would like to thank Dr. Hsiung-Fei Chien for providing medical support. We would like to thank Dr. Ching-Wen Lin, Dr. Min-Liang Kuo, Hui-Ju Ho, and Yu-Ting Kuo for their editing service on the English version of the manuscript.

## Statement of Ethics

The research was conducted in ethical accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the caregivers for the publication of this case report and any accompanying images. A copy of the written consent is available for review from the Editor of this journal.

## Author Contributions

YHY data collection, data analysis, and data interpretation; CMP data collection and wrote the manuscript.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

## References

- [1] Cho, N.H., Shaw, J.E., Karuranga, S., *et al.* (2018) IDF Diabetes Atlas: Global Estimates of Diabetes Prevalence for 2017 and Projections for 2045. *Diabetes Research and Clinical Practice*, **138**, 271-281. <https://doi.org/10.1016/j.diabres.2018.02.023>
- [2] Cole, J.B. and Florez, J.C. (2020) Genetics of Diabetes Mellitus and Diabetes Complications. *Nature Reviews Nephrology*, **16**, 377-390. <https://doi.org/10.1038/s41581-020-0278-5>
- [3] Nacak, H., Bolignano, D., Van Diepen, M., *et al.* (2016) Timing of Start of Dialysis in Diabetes Mellitus Patients: A Systematic Literature Review. *Nephrology Dialysis Transplantation*, **31**, 306-316. <https://doi.org/10.1093/ndt/gfv431>
- [4] Alalawi, F. and Bashier, A. (2021) Management of Diabetes Mellitus in Dialysis Pa-

- tients: Obstacles and Challenges. *Diabetology & Metabolic Syndrome*, **15**, 1025-1036. <https://doi.org/10.1016/j.dsx.2021.05.007>
- [5] Armstrong, D.G., Boulton, A.J.M. and Bus, S.A. (2017) Diabetic Foot Ulcers and Their Recurrence. *The New England Journal of Medicine*, **376**, 2367-2375. <https://doi.org/10.1056/NEJMra1615439>
- [6] Schaper, N.C., van Netten, J.J., Apelqvist, J., *et al.* (2020) Practical Guidelines on the Prevention and Management of Diabetic Foot Disease (IWGDF 2019 Update). *Diabetes/Metabolism Research and Reviews*, **36**, e3266. <https://doi.org/10.1002/dmrr.3266>
- [7] Ndip, A., Rutter, M.K., Vileikyte, L., *et al.* (2010) Dialysis Treatment Is an Independent Risk Factor for Foot Ulceration in Patients with Diabetes and Stage 4 or 5 Chronic Kidney Disease. *Diabetes Care*, **33**, 1811-1816. <https://doi.org/10.2337/dc10-0255>
- [8] Game, F.L., Chipchase, S.Y., Hubbard, R., *et al.* (2006) Temporal Association between the Incidence of Foot Ulceration and the Start of Dialysis in Diabetes Mellitus. *Nephrology Dialysis Transplantation*, **21**, 3207-3210. <https://doi.org/10.1093/ndt/gfl427>
- [9] Maroz, N. (2016) Impact of Renal Failure on Wounds Healing. *Journal of the American College of Clinical Wound Specialists*, **8**, 12-13. <https://doi.org/10.1016/j.jccw.2018.01.004>
- [10] Lavery, L.A., Lavery, D.C., Hunt, N.A., *et al.* (2015) Amputations and Foot-Related Hospitalisations Disproportionately Affect Dialysis Patients. *International Wound Journal*, **12**, 523-526. <https://doi.org/10.1111/iwj.12146>
- [11] Honda, Y., Hirano, K., Yamawaki, M., *et al.* (2017) Wound Healing of Critical Limb Ischemia with Tissue Loss in Patients on Hemodialysis. *Vascular*, **25**, 272-282. <https://doi.org/10.1177/1708538116673015>
- [12] Dugbartey, G.J. and Alornyo, K.K. (2022) Association between Diabetic Kidney Disease and Diabetic Foot Ulceration. In: Raghav, A., Ed., *Diabetic Foot—Recent Advances*, IntechOpen, London. <https://doi.org/10.5772/intechopen.107825>
- [13] He, Y., Qian, H., Xu, L., *et al.* (2017) Association between Estimated Glomerular Filtration Rate and Outcomes in Patients with Diabetic Foot Ulcers: A 3-Year Follow-Up Study. *European Journal of Endocrinology*, **177**, 41-50. <https://doi.org/10.1530/EJE-17-0070>
- [14] Lin, C.W., Chen, C.C., Huang, W.Y., *et al.* (2022) Restoring Prohealing/Remodeling-Associated M2a/c Macrophages Using ON101 Accelerates Diabetic Wound Healing. *JID Innovations*, **2**, Article 100138. <https://doi.org/10.1016/j.xjidi.2022.100138>
- [15] Huang, Y.Y., Lin, C.W., Cheng, N.C., *et al.* (2021) Effect of a Novel Macrophage-Regulating Drug on Wound Healing in Patients with Diabetic Foot Ulcers: A Randomized Clinical Trial. *JAMA Network Open*, **4**, e2122607. <https://doi.org/10.1001/jamanetworkopen.2021.22607>
- [16] Krediet, R.T. and Parikova, A. (2022) Relative Contributions of Pseudohypoxia and Inflammation to Peritoneal Alterations with Long-Term Peritoneal Dialysis Patients. *Clinical Journal of the American Society of Nephrology*, **17**, 1259-1266. <https://doi.org/10.2215/CJN.15371121>
- [17] Nassar, G.M. (2013) Preventing and Treating Inflammation: Role of Dialysis Access Management. *Seminars in Dialysis*, **26**, 28-30. <https://doi.org/10.1111/sdi.12023>
- [18] Velloso, M.S., Otoni, A., de Paula Sabino, A., *et al.* (2014) Peritoneal Dialysis and Inflammation. *Clinica Chimica Acta*, **430**, 109-114.



- <https://doi.org/10.1016/j.cca.2013.12.003>
- [19] Maroz, N. and Simman, R. (2013) Wound Healing in Patients with Impaired Kidney Function. *Journal of the American College of Clinical Wound Specialists*, **5**, 2-7. <https://doi.org/10.1016/j.jccw.2014.05.002>
- [20] Klinger, M. and Madziarska, K. (2019) Mortality Predictor Pattern in Hemodialysis and Peritoneal Dialysis in Diabetic Patients. *Advances in Clinical and Experimental Medicine*, **28**, 133-135. <https://doi.org/10.17219/acem/76751>