Oral Statin Therapy in KRT16- and KRT17-Associated Palmoplantar Epidermal Differentiation Disorder (Pachyonychia Congenita)

Running head: Oral statins for KRT16/KRT17-pEDD-PC

Sota Itamoto[1]†, Wei-Ting Tu[2]†, Chih-Yu Chang[2], Mika Watanabe[1], Hideyuki Ujiie[1], Chao-Kai Hsu[2,3]*, Ken Natsuga[1]*

[1]Department of Dermatology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan

[2]Department of Dermatology, National Cheng Kung University Hospital, Tainan, Taiwan

[3]International Center for Wound Repair and Regeneration (iWRR), National Cheng Kung University, Tainan, Taiwan.

†These authors contributed equally to this work.

*Correspondence:

Chao-Kai Hsu, M.D., Ph.D.

Department of Dermatology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, 138 Sheng-Li Rd, Tainan, Taiwan

E-mail: kylehsu@mail.ncku.edu.tw

Tel: +886-6-2353535-5415

Ken Natsuga, M.D., Ph.D.

Department of Dermatology, Faculty of Medicine and Graduate School of Medicine Hokkaido University, N15W7, Sapporo 060-8638, Japan

E-mail: natsuga@med.hokudai.ac.jp

Tel: +81-11-706-7387

Funding information: The National Cheng Kung University Hospital Grant.

Conflicts of Interest: H. Ujiie is an Editorial Board member of the Journal of Dermatology and a co-author of this article. To minimize bias, he was excluded from all

editorial decision-making related to the acceptance of this article for publication.

Ethical Approval: Reviewed and approved by the institutional review board of Hokkaido University Hospital (#92), Hokkaido University Graduate School of Medicine (#14-063), and National Cheng Kung University Hospital (B-BR-110-100, NCKUH-11104017).

Ethics statement: The patients have given written informed consent to the publication of their case details.

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abstract word count: 132 words

Manuscript word count: 1093 words [including abstract]

References: 15

Figures: 1

Tables: 1

Keywords: Pachyonychia congenita, Calluses, Rosuvastatin, Pitavastatin, Atorvastatin

Abstract

Palmoplantar epidermal differentiation disorder associated with pachyonychia congenita (pEDD-PC) is a rare autosomal dominant skin disorder caused by pathogenic variants in keratin genes, including *KRT6A*, *KRT6B*, *KRT6C*, *KRT16* and *KRT17*. While statins have been reported to alleviate symptoms in *KRT6A*-pEDD-PC, their efficacy in other subtypes remains unclear. We report six adult patients, including four with *KRT17* variants and two with *KRT16* variants, who underwent off-label oral statin therapy. Statins were administered for at least six months following dose stabilization. Although the treatment was well tolerated in most cases, no significant clinical improvement in plantar calluses or pain was observed. All patients discontinued therapy due to insufficient efficacy. Our findings indicate that oral statin therapy may offer limited benefit in *KRT16*/*KRT17*-pEDD-PC and suggest the potential importance of early intervention and genotype-specific therapeutic strategies.

INTRODUCTION

Palmoplantar epidermal differentiation disorder associated with pachyonychia congenita (pEDD-PC)[1], formerly known as pachyonychia congenita, is an autosomal dominant skin disorder characterized by nail dystrophy, plantar calluses, and sebaceous cysts (steatocystoma multiplex). Diagnosis of pEDD-PC is based on clinical findings and/or identification of a heterozygous pathogenic variant in one of five keratin genes associated with the disease: *KRT6A*, *KRT6B*, *KRT6C*, *KRT16*, and *KRT17*, encoding keratins 6A, 6B, 6C, 16, and 17, respectively. The disease is further subclassified into *KRT6A/KRT6B/KRT6C/KRT16/KRT17*-pEDD-PC, according to the specific gene variant present in each patient.

pEDD-PC imposes substantial psychological and economic burdens on affected individuals, primarily due to severe plantar pain from calluses. Accordingly, there is a growing need for treatments that effectively alleviate this pain and improve patients' quality of life. Various therapeutic agents have been explored for pEDD-PC, including reports demonstrating the efficacy of oral statins, which are hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, in treating patients with *KRT6A*-pEDD-PC[2, 3, 4]. Here, we present our experience with oral statin therapy in adult patients from one *KRT17*-pEDD-PC family and one *KRT16*-pEDD-PC family.

MATERIALS AND METHODS

Off-label oral statin therapy was administered to four patients with *KRT17*-pEDD-PC (Patients 1-4), each harboring a heterozygous c.296T>C (p.Leu99Pro) variant in *KRT17* from a single family[5], and two patients with *KRT16*-pEDD-PC (Patients 5-6), each harboring a heterozygous c.374A>G (p.Asn125Ser) variant in *KRT16*, also from a single family (**Table 1**). The off-label use of statins and data collection were approved by the Institutional Review Board of Hokkaido University Hospital (#92), Hokkaido University Graduate School of Medicine (#14-063), and National Cheng Kung University Hospital (B-BR-110-100, NCKUH-11104017). The study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from the subjects prior to data collection.

Treatment was primarily with rosuvastatin. Rosuvastatin was initiated at 5 mg/day and gradually increased to 10–20 mg/day, with monthly blood tests to monitor blood counts, creatine kinase, liver function, and renal function. Approximately six months after dose stabilization, the size and pain intensity of plantar calluses were evaluated. Pain intensity was assessed using the visual analog scale (VAS). Only Patient 6 received a different regimen: pitavastatin 2 mg/day for 6 months followed by atorvastatin 10-20 mg/day for 15 months.

RESULTS

All patients completed at least six months of oral statin treatment following dose stabilization. Patients 2-4 were able to increase the rosuvastatin dose to 20 mg. Patient 1 required a dose reduction to 10 mg due to elevated serum creatine kinase levels when the dose was increased to 15 mg. The final dose for Patient 5 was also 10 mg. Patients 2-6 did not experience any adverse effects. Table 1 summarizes the VAS scores of all patients before and after the treatment, showing no substantial improvement. Similarly, the clinical manifestations of the plantar calluses remained largely unchanged in all cases (**Figure 1**). Given the limited efficacy, oral statin treatment was discontinued.

DISCUSSION

pEDD-PC-associated genes encode stress-induced keratin proteins, which serve as crucial intermediate filaments in areas subjected to mechanical stress. Dominant negative effects resulting from heterozygous variants in these keratin genes are thought to compromise the mechanical stability of epithelial cells, such as those in the

nail unit and palmoplantar epidermis. Statins may alleviate these effects by reducing the expression of *KRT6A*.

The most commonly used treatment for plantar pain in pEDD-PC is mechanical shaving of the calluses. This method, also used for calluses in the general population, has the advantage of being easily administered in any setting; however, its efficacy is temporary. Traditional topical treatments, including keratolytics, emollients, retinoids, and steroids, are not highly effective. Systemic administration of retinoids can inhibit hyperkeratosis, but long-term use is often limited by adverse effects.

In recent years, several new treatments have been reported, including intradermal injection of botulinum toxin[6] and oral erlotinib[7], partly due to the efforts of Pachyonychia Congenita Project (PC Project), an international patient advocacy organization. Rapamycin has been shown to selectively inhibit *KRT6A* expression in cultured human keratinocytes, and its topical application improved symptoms in two pEDD-PC cases. However, according to a press release from Palvella Therapeutics, a phase 3 trial using topical rapamycin did not meet a primary endpoint, which was a daily patient-reported outcome measure[8]. Furthermore, although systemic rapamycin has shown symptom improvement in pEDD-PC patients, treatment discontinuation is often necessary due to adverse effects[9]. As a specific treatment, injection of siRNA targeting the pathogenic

KRT6A variant mRNA, without affecting wild-type *KRT6A,* has shown improvement in calluses in a *KRT6A*-pEDD-PC patient[9].

Simvastatin, an HMG-CoA reductase inhibitor, reduces *KRT6A* gene expression by binding to a specific site in its promoter region[10]. This *KRT6A* inhibition by statins is partially dependent on the Stat1 transcription factor. Our rationales for oral statin therapy for *KRT16*/*KRT17*-pEDD-PC patients include: 1) previously reported efficacy in *KRT6A*-pEDD-PC patients[2, 3, 4], 2) heterodimer formation of keratins 6 and 16[11], and 3) STAT1-dependent regulation of *KRT17* expression[12]. Although some patients showed a mild reduction in VAS scores, all eventually discontinued treatment due to unsatisfactory outcomes. The limited efficacy may be attributed to minimal (direct or indirect) effects of statins on *KRT16*/*KRT17* expression, insufficient drug concentration at the target site, or it may reflect the older age of our patients compared to previously reported pediatric and young adult *KRT6A*-pEDD-PC cases[2, 3, 4]. Statins may be more effective when initiated at earlier ages[13]. Additionally, Nrf2, a known inducer of both *KRT16* and *KRT17* expression[14], is activated by statins[15]. This raises the possibility that the Nrf2-mediated upregulation of *KRT16* and *KRT17* may have offset their suppression caused by the mechanism described above. One of the limitations of this case series is its small size. It remains uncertain whether the same lack of efficacy

would be observed in other families with KRT16/KRT17-pEDD-PC. Our study suggests that therapies other than oral statins may be more beneficial for adult patients with *KRT16*/*KRT17*-pEDD-PC.

REFERENCES

1. Sprecher E, Ishida-Yamamoto A, Schwartz J, Akiyama M, Aldwin-Easton M, Choate K, et al., “Palmoplantar epidermal differentiation disorders: a new classification towards pathogenesis-based therapy,” *British Journal of Dermatology*, (2025): ljaf054, https://doi.org/10.1093/bjd/ljaf054.

2. Abdollahimajd F, Rajabi F, Shahidi-Dadras M, Saket S, Youssefian L, Vahidnezhad H, et al., “Pachyonychia congenita: a case report of a successful treatment with rosuvastatin in a patient with a KRT6A mutation,” *The British journal of dermatology* 181, no. 3 (2019): 584-586, https://doi.org/10.1111/bjd.17276.

3. Zhao Y, Gartner U, Smith FJ, McLean WH, “Statins downregulate K6a promoter activity: a possible therapeutic avenue for pachyonychia congenita,” *The Journal of investigative dermatology* 131, no. 5 (2011), 1045–1052, https://doi.org/10.1038/jid.2011.41.

4. Frommherz L, Has C, “Successful treatment of Pachyonychia congenita with Rosuvastatin,” *Journal of the European Academy of Dermatology and Venereology* 34, no. 9 (2020): e480-e482, https://doi.org/10.1111/jdv.16393.

5. Kanda M, Natsuga K, Nishie W, Akiyama M, Nagasaki A, Shimizu T, et al.,

"Morphological and genetic analysis of steatocystoma multiplex in an Asian family with pachyonychia congenita type 2 harbouring a KRT17 missense mutation," *The British journal of dermatology 160*, no. 2 (2009): 465–468, https://doi.org/10.1111/j.1365-2133.2008.08983.x.

6. Koren A, Sprecher E, Reider E, Artzi O, "A treatment protocol for botulinum toxin injections in the treatment of pachyonychia congenita-associated keratoderma," *The British journal of dermatology* 182, no. 3 (2020): 671–677, https://doi.org/10.1111/bjd.18169.

7. Basset J, Marchal L, Hovnanian A, "EGFR Signaling Is Overactive in Pachyonychia Congenita: Effective Treatment with Oral Erlotinib," *The Journal of investigative dermatology* 143, no. 2 (2023): 294–304, https://doi.org/10.1016/j.jid.2022.08.045.

8. Wesley, Kaupinen. "Palvella Therapeutics Reports Topline Results from Pivotal Phase 3 VAPAUS Study of QTORIN™ 3.9% Rapamycin Anhydrous Gel (QTORIN™ rapamycin) for the Treatment of Pachyonychia Congenita" Palvella Therapeutics, 20 July, 2023. palvellatx.com/2023/07/20/palvella-therapeutics-reports-topline-results-from-pivotal-phase-3-vapaus-study-of-qtorin-rapamycin-pachyonychia-congenita. Accessed May 6, 2025.

9. Leachman SA, Hickerson RP, Schwartz ME, Bullough EE, Hutcherson SL, Boucher KM, et al., “First-in-human mutation-targeted siRNA phase Ib trial of an inherited skin disorder,” *Molecular therapy : the journal of the American Society of Gene Therapy* 18, no. 2 (2010): 442–446, https://doi.org/10.1038/mt.2009.273.

10. Sharma S, Dayal S, Aggarwal K, Gowda V M V, Kaur R, “Scrutinising the role of simvastatin in a patient of Pachyonychia Congenita with KRT6A gene mutation,” *The Australasian journal of dermatology* 63, no.2 (2022): e145–e149, https://doi.org/10.1111/ajd.13835.

11. Coulombe PA, Wawersik M, Paladini RD, Noensie E, “Type I keratin 16 forms relatively unstable tetrameric assembly subunits with various type II keratin partners: biochemical basis and functional implications,” *The Biological bulletin* 194, no. 3 (1998): 364–366, https://doi.org/10.2307/1543114.

12. Shi X, Jin L, Dang E, Chang T, Feng Z, Liu Y, et al. IL-17A upregulates keratin 17 expression in keratinocytes through STAT1- and STAT3-dependent mechanisms. J Invest Dermatol. 2011;131:2401-8.

13. O'Toole EA, Kelsell DP, Caterina MJ, de Brito M, Hansen D, Hickerson RP, et al., “Pachyonychia Congenita: A Research Agenda Leading to New Therapeutic

Approaches," *The Journal of investigative dermatology* 144, no. 4 (2024): 748–754, https://doi.org/10.1016/j.jid.2023.10.030.

14. Yang L, Fan X, Cui T, Dang E, Wang G., "Nrf2 Promotes Keratinocyte Proliferation in Psoriasis through Up-Regulation of Keratin 6, Keratin 16, and Keratin 17," *The Journal of investigative dermatology* 137, no. 10 (2017): 2168-2176, doi:10.1016/j.jid.2017.05.015.

15. Mansouri A, Reiner Ž, Ruscica M, Tedeschi-Reiner E, Radbakhsh S, Bagheri Ekta M, et al., "Antioxidant Effects of Statins by Modulating Nrf2 and Nrf2/HO-1 Signaling in Different Diseases," *Journal of clinical medicine* 11, no. 5 (2022): 1313, doi:10.3390/jcm11051313.

FIGURE LEGENDS

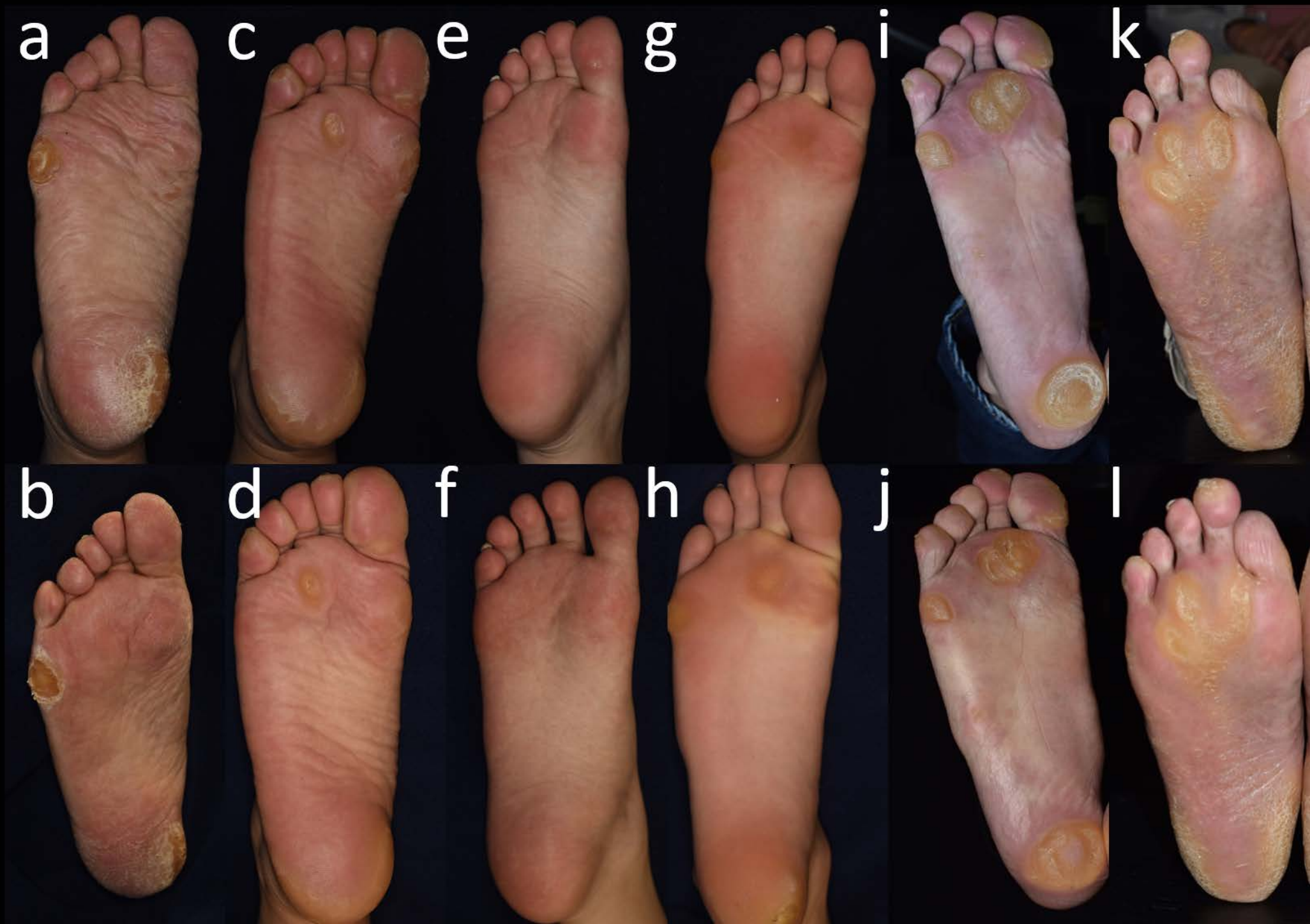
Fig. 1. Clinical manifestations before and after oral statin therapy.

(**a, b**) Patient 1; (**c, d)** Patient 2; (**e, f**) Patient 3; (**g, h**) Patient 4; (**i, j**) Patient 5; (**k, l**) Patient 6. Images before treatment (**a, c, e, g, i, k**); after (**b, d, f, h, j, l**) treatment.

Table. 1. Overview of pEDD-PC patients treated with statins.

	Family 1				Family 2	
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age/Sex	80/M	54/F	21/F	17/M	30/M	54/F
Variant	Heterozygous c.296T>C in *KRT17*				Heterozygous c.374A>G in *KRT16*	
Pre-treatment VAS score	6.4	7.3	10	8.4	4.5	Moderate to severe pain†
Post-treatment VAS sccore	4.4	7.0	3.5	5.9	8	No improvement†

†VAS score not documented in the medical record.


a
c
e
g
i
k
b
d
f
h
j
l