Divalproex sodium: A potential therapy for scleroderma digital ulcers

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INTRODUCTION

Scleroderma is an autoimmune connective tissue disease that involves the skin and internal organs for which there are few reliably effective treatments.[1] The cutaneous manifestations of scleroderma include fibrosis and sclerodactyly, calcinosis cutis, digital ulcers, pigmentary changes, and mat telangiectasias. Three major pathways are thought to be important in the pathogenesis of scleroderma: autoimmunity and inflammation, microvascular alteration, and fibrosis.[2] Although immunosuppression (eg, methotrexate[3]) and vasodilatory therapy (eg, nifedipine[4]) are commonly used to address the inflammatory and microvascular components, respectively, therapy directed at tissue fibrosis has remained elusive. Histone deacetylase inhibitors (HDACi) may have antifibrogenic effects in the skin and other organs via mediation of transforming growth factor beta (TGF-β).[5-7] Divalproex sodium has known activity as an HDACi.[8]

We report the therapeutic outcome of a patient treated with the HDACi, divalproex sodium.

Abbreviations used:

ER:	extended release
HDACi:	Histone deacetylase inhibitor
TSA:	trichostatin A
TGF-β:	Transforming growth factor beta

CASE REPORT

A 62-year-old woman with an 8-year history of limited scleroderma presented with painful ulcers involving the fingers that typically recurred every 2 to 4 months. For the previous year she had taken a stable regimen of rituximab, hydroxychloroquine, nifedipine, lisinopril, colchicine, aspirin, prednisone, and gabapentin. Examination of her skin revealed pink-red erythema of the hands, peeling and fissuring of the palms and digits, and mild tapering of the distal fingers. Treatment with divalproex sodium extended release (ER) 250 mg daily was initiated, and over the next 4 months she did not experience digital ulcers and reported decreased swelling of her fingers and improvement in her ability to grasp objects. During this time the complete blood cell count with differential, complete metabolic panel, and valproic acid level did not show hyperglycemia, thrombocytopenia, hepatotoxicity, abnormally high valproic acid level, or any other abnormality. The potential benefit of divalproex sodium was questioned after the development of a digital pit (although it was smaller and less painful than her usual ones and appeared to heal more quickly), and so the medication was discontinued after 6 months of treatment. Within weeks of discontinuing divalproex sodium the patient developed 4 painful digital ulcers (Fig 1, *A* and *B*). Divalproex sodium ER 250 mg daily was restarted, and the ulcers healed (Fig 1, *C* and *D*). One and a half years later, at the time of writing this report, the patient continues to take divalproex sodium ER 250 mg daily without a single recurrence of digital ulcers and with stable improvement in grasp function. Notably, treatment with divalproex sodium has not affected her Raynaud's symptoms or frequency of attacks.

DISCUSSION

Scleroderma is a complex disease, and although its pathogenesis is incompletely understood, TGF-β is thought to be important.[2] Immunosuppressive

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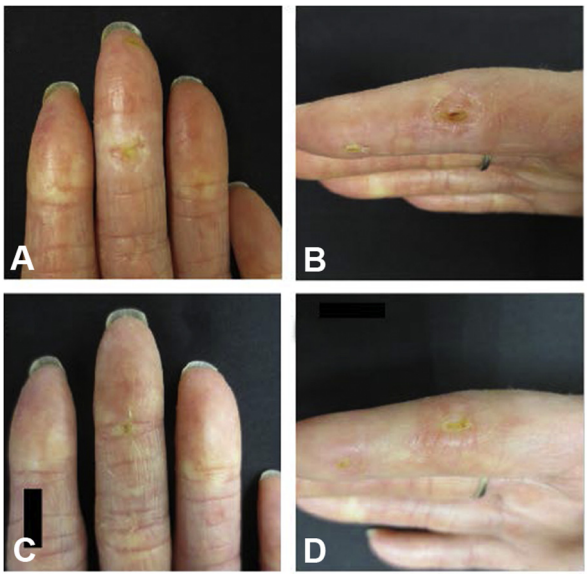

Fig 1. Scleroderma digital ulcers. Ulcers on the (**A**) volar left third digit and (**B**) the lateral right second digit occurring within weeks of discontinuation of divalproex sodium. Re-epithelialization of the ulcers (**C** and **D**) after 2 months of therapy.

and vasodilatory agents are currently the mainstays of therapy, although other agents are often used.

The use of divalproex sodium in our patient was based on its properties as an HDACi.[8,9] Histone deacetylase inhibition has been shown to have antifibrogenic effects in the skin and other organs via mediation of TGF-β.[5-7] The HDACi trichostatin A (TSA) reduced expression of fibrosis-related genes and blocked the stimulatory effect of TGF-β1 on procollagen α1 transcription in rat skin fibroblasts in vitro.[6] In another study, the addition of TSA to nuclear extracts from scleroderma fibroblasts normalized collagen expression when compared with normal skin fibroblasts.[7] Additionally, treatment of human lung fibroblasts with TSA inhibited both TGF-β1–mediated α-smooth muscle actin and α1 type I collagen mRNA induction, and the differentiation of cultured normal human lung fibroblasts to myofibroblasts was shown to be an HDAC4-dependent process.[5] In another study of human pulmonary fibroblasts, phenylbutyrate, an HDACi, decreased collagen type I production.[10]

We report remission of digital ulcers in a patient with limited scleroderma treated with divalproex sodium. Further evidence of the positive effect of divalproex sodium in this patient was the recurrence of ulcers after discontinuing treatment followed again by remission after restarting treatment.

Divalproex sodium may be beneficial for the treatment of the digital ulcerations of scleroderma. We hypothesize that the HDACi activity of divalproex sodium, via mediation of TGF-β signaling,[5-7] mitigates fibrosis, which contributes to digital ulcers (together with vasospasm from Raynaud's and microvascular alteration). Further studies are necessary to more objectively evaluate the role of divalproex sodium in the treatment of scleroderma, and a clinical trial is currently underway (ClinicalTrials.gov NCT02166229).

REFERENCES

1. Kowal-Bielecka O, Landewe R, Avouac J, et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Ann Rheum Dis*. 2009;68(5):620-628.
2. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. *N Engl J Med*. 2009;360(19):1989-2003.
3. Kroft EB, Creemers MC, van den Hoogen FH, Boezeman JB, de Jong EM. Effectiveness, side-effects and period of remission after treatment with methotrexate in localized scleroderma and related sclerotic skin diseases: an inception cohort study. *Br J Dermatol*. 2009;160(5):1075-1082.
4. Thomas RHM, Rademaker M, Grimes SM, et al. Nifedipine in the Treatment of Raynauds-Phenomenon in Patients with Systemic-Sclerosis. *Br J Dermatol*. 1987;117(2):237-241.
5. Guo WC, Shan B, Klingsberg RC, Qin XM, Lasky JA. Abrogation of TGF-beta 1-induced fibroblast-myofibroblast differentiation by histone deacetylase inhibition. *Am J Physiol Lung Cell Mol Physiol*. 2009;297(5):L864-L870.
6. Rombouts K. Trichostatin A, a Histone Deacetylase Inhibitor, Suppresses Collagen Synthesis and Prevents TGF-β1-Induced Fibrogenesis in Skin Fibroblasts. *Exp Cell Res*. 2002;278(2):184-197.
7. Wang YQ, Fan PS, Kahaleh B. Association between enhanced type I collagen expression and epigenetic repression of the FLI1 gene in scleroderma fibroblasts. *Arthritis Rheum*. 2006;54(7):2271-2279.
8. Gurvich N, Tsygankova OM, Meinkoth JL, Kein PS. Histone deacetylase is a target of valproic acid-mediated cellular differentiation. *Cancer Res*. 2004;64(3):1079-1086.
9. Gottlicher M, Minucci S, Zhu P, et al. Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. *EMBO J*. 2001;20(24):6969-6978.
10. Rishikof DC, Ricupero DA, Liu H, Goldstein RH. Phenylbutyrate decreases type I collagen production in human lung fibroblasts. *J Cell Biochem*. 2004;91(4):740-748.