Apremilast as an adjuvant therapy for calcinosis cutis

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Key words: apremilast; calcinosis cutis; CREST; dystrophic calcification; limited scleroderma; morphea; persistent; potential; therapeutic substance; treatment.

INTRODUCTION
Calcinosis cutis is a form of dystrophic calcification wherein hydroxyapatite and amorphous calcium phosphate deposits form over damaged subcutaneous tissues despite normal serum Ca\(^{2+}\), PO\(_4^{3-}\)/CO\(_2\), and parathyroid hormone (PTH) levels.\(^{1,2}\) When it is widespread, major morbidity from restricted movement and pain are the primary presenting symptoms. Treatments reported include calcium binders (minocycline), calcium channel blockers, surgical excision, lithotripsy, and the calciomimetic sodium thiosulfate in topical, intraleisional, or systemic form.\(^{3,5}\) Cutaneous calcification in these patients occurs due to damaged tissue releasing phosphate-binding proteins that bind serum phosphate, with subsequent precipitation of calcium salts in the tissue.\(^{2}\) In this study, we review 2 patients with recalcitrant calcinosis cutis who responded to apremilast after not responding to multiple other modalities to help mobilize calcium.

CASE REPORT 1
A 66-year-old woman with a medical history of morphea, monoclonal gammopathy of undetermined significance, alopecia areata, osteoarthritis, diabetes, and hypertension, presented in 2016 with progressive calcinosis cutis within and beyond areas affected by the morphea of both lower legs (Fig 1). Her current treatments were methotrexate (25 mg/wk for 1 year), calcipotriene, and clobetasol ointments. Physical examination found confluent and nearly plate-like circumferential indurated plaques covering the lower half of both legs. Serum chemistries including Ca\(^{2+}\), PO\(_4^{3-}\), and PTH were normal. Over the next year, treatments included daily topical sodium thiosulfate 25% w/v (topical in emollient base), pentoxifylline (oral), minocycline (oral), amiodipine (oral), percutaneous ultrasonic lithotripsy (30 treatments), and a series of 10 weekly injections of intraleisional sodium thiosulfate (150 mg/mL × 5 mL/wk). There was minimal improvement over this time. She started on apremilast in 2017 and within 2 months began to notice improvement.

Over the next 3 to 6 months, she had had numerous pinpoint erosions with central jagged calcium fragments. Many of these required sharp surgical debridement to remove. Resulting ulcerations required several courses of oral antibiotics due to secondary infection. Apremilast was ultimately decreased to 30 mg once daily, but infections continued to occur. The confluent plaques progressively became more broken up with palpable spaces of normal skin intervening. Despite this clinical improvement, the patient noticed new areas of proximal calf induration. Apremilast was ultimately discontinued because of the recurrent infections within the ulcerated areas of calcification.

CASE REPORT 2
A 59-year-old woman with a medical history of CREST (calcinosis, Raynaud phenomenon,
esophageal dysmotility, sclerodactyly, and telangiec-
tasia) syndrome, rheumatoid arthritis (RA), stasis
dermatitis, obesity, and venous ulcers presented in
2016 with generalized pain and diffuse plate-like
induration of both lower extremities (Fig 2). She had
been treated for 2 years with weekly methotrexate
(25 mg subcutaneous) injections for her RA and
CREST. Skin biopsy and radiograph confirmed wide-
spread subcutaneous calcification, and there were no
serum abnormalities of Ca²⁺, PO₄³⁻, creatinine, or
PTH. She was initially treated with sodium thiosulfate
25% w/v (topical in emollient base) and diltiazem
(240 mg/d oral). Over the next 3 months, she noted
many bumps and a recurrent ulcer on the right
posterior calf, but no other change in the condition.
Pentoxifylline and minocycline were added, and a
series of subcutaneous sodium thiosulfate (150 mg/
ml) injections led to some areas of softening and
separation within the original confluent plaques of
calcification. Apremilast was added for her RA in 2017,
and she slowly had softening of the plates of calcifi-
cation and numerous pinpoint papules with central
jagged calcium fragments being extruded. Sharp sur-
gical debridement was required to facilitate removal of
calcium fragments. She remains on apremilast with
slow improvement, and calf ulcerations have healed.
No infectious complications have been noted.

**DISCUSSION**

Apremilast is a phosphodiesterase 4 (PDE-4) inhibitor approved for the treatment of rheumatoid arthritis, psoriasis, and psoriatic arthritis.⁹ Its mechanism of action involves reducing PDE-4, which acts
to breakdown cyclic adenosine monophosphate (cAMP). Increased levels of cAMP downregulate numerous proinflammatory factors including tumor necrosis factor-α, interleukin (IL)-17, and IL-23 and upregulates the anti-inflammatory cytokine IL-10.⁷ The mechanism of action of apremilast in patients with calcinosis cutis is unknown, but its ability to
downregulate proinflammatory cytokines seems
likely to be central. Elevated proinflammatory medi-
ators have been implicated as a main cause of
calcinosis cutis, possibly via chronic tissue damage
and/or vascular hypoxia. This finding results in
tissue fibrosis and increase PO₄³⁻ binding, which
becomes a scaffold for calcification. Inflammatory
cytokines such as tumor necrosis factor, IL-6, and IL-
1β contribute to the formation of calcium salts in the
tissue and are a driving force to the cutaneous
manifestations of calcinosis cutis.⁸

Although these 2 patients represent anecdotal
reports, an intriguing hypothetical mechanism is
proposed. We look forward to future clinical trials
of PDE-4 inhibitors in extensive calcinosis cutis to
help elucidate these mechanisms.

**REFERENCES**

1. Muddegowda PH, Lingegowda JB, Ramachandrarao RK, Konapur PG. Calcinosis cutis: report of 4 cases. J Lab Physicians. 2011;3(2):125-126.
2. Le C, Bedocs PM. Calcinosis Cutis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2019. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448127/.
3. Reiter N, El-Shabraw L, Leinweber B, Berghold A, Aberer E. Calcinosis cutis: part II. Treatment options. J Am Acad Dermatol. 2011;65(1):15-22.
4. Valenzuela A, Chung L. Calcinosis: pathophysiology and management. *Curr Opin Rheumtol*. 2015;27(6):542-548.
5. Bair B, Fivenson D. A novel treatment for ulcerative calcinosis cutis. *J Drugs Dermatol*. 2011;10(9):1042-1044.
6. Schafer PH, Day RM. Novel systemic drugs for psoriasis: mechanism of action for apremilast, a specific inhibitor of PDE4. *J Am Acad Dermatol*. 2013;68(6):1041-1042.
7. Hoeltzel MF, Oberle EJ, Robinson AB, Agarwal A, Rider LG. The presentation, assessment, pathogenesis, and treatment of calcinosis in juvenile dermatomyositis. *Curr Rheumatol Rep*. 2014;16(12):467.
8. Shimizu M, Ueno K, Ishikawa S, Kasahara Y, Yachie A. Role of activated macrophage and inflammatory cytokines in the development of calcinosis in juvenile dermatomyositis. *Rheumatol*. 2014;53(4):766-767.