Apremilast as an adjuvant therapy for calcinosis cutis

Introduction: Calcinosis cutis is a form of dystrophic calcification wherein hydroxyapatite and amorphous calcium phosphate deposits form over damaged subcutaneous tissues despite normal serum $Ca^{2+}$, $PO_4^{3-}$, and parathyroid hormone (PTH) levels. In this study, we review 2 patients with recalcitrant calcinosis cutis who responded to apremilast after failing multiple other modalities to help mobilize calcium.

Case presentations: A 66 year old female with past medical history of morphea, monoclonal gammopathy of undetermined significance (MGUS), 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. She started on apremilast in 2017 and, within two months, began to notice improvement. Apremilast was ultimately discontinued due to the recurrent infections within the ulcerated areas of calcification.

A 59 year old female with a past medical history of CREST 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. She had been treated for 2 years with weekly methotrexate (25 mg subcutaneous) injections for her RA and CREST. Apremilast was added for her RA in 2017 and she slowly developed softening of the plates of calcifications and numerous pinpoint papules with central jagged calcium fragments being extruded. Sharp surgical 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. 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 mediators have been implicated as a main cause of calcinosis cutis, possibly via chronic tissue damage and/or vascular hypoxia. This results in tissue fibrosis and increase $PO_4^{3-}$ binding, which becomes a scaffold for calcification. While these 2 patients represent anecdotal reports, an intriguing hypothetical mechanism is proposed.