Successful treatment of severe chronic cutaneous lupus with anifrolumab: A series of 6 cases

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Key words: anifrolumab; chronic cutaneous lupus; cutaneous lupus; discoid lupus; lupus; type I interferon.

INTRODUCTION

Cutaneous lupus erythematosus (CLE) is a chronic autoimmune condition that encompasses several subtypes with varying morphologies but a shared pathogenesis and cytokine signature.[1,2] CLE is often isolated to the skin; an additional 70% to 80% of patients with systemic lupus erythematosus (SLE) suffer from CLE during their disease course.[3,4] Given its potential for permanent scarring and dyspigmentation, CLE carries a significant negative impact on quality of life.[5,6] Management of CLE subtypes has traditionally consisted of preventive measures alongside combinations of topical and systemic immunosuppressive therapies. First line treatments consist of topical or intralesional steroids and antimalarials. Treatment progression with potent immunosuppressants is unfortunately common as many patients are inadequately treated with monotherapy.[7] There is a paucity of clinical trials evaluating therapies specifically for CLE. Most medications used to treat CLE in our current armamentarium have been adapted from SLE treatments. This becomes problematic as efficacy has been assessed in systemic but not cutaneous disease and in recalcitrant cases the therapeutic ladder is often uncertain. Type I interferons (IFNs) are key mediators of the inflammatory cascade of CLE and have been shown to be present in high levels in both the blood and the skin.[1] Recently, there have been several reports as well as a small prospective trial describing the efficacy of the anti-type I IFN receptor (IFNAR1) monoclonal antibody anifrolumab (ANI) for cutaneous lupus.[8-12] To further support the use of ANI for the treatment of recalcitrant CLE, irrespective of SLE diagnosis, we report our experience in 6 patients with severe chronic cutaneous lupus erythematosus (CCLE) treated at the University of Rochester Medical Center.

Abbreviations used:

ANI:	anifrolumab
AZA:	azathioprine
CCLE:	chronic cutaneous lupus erythematosus
CLASI-A:	Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity
CLE:	cutaneous lupus erythematosus
CQ:	chloroquine
CSA:	cyclosporine
CTX:	cyclophosphamide
DLE:	discoid lupus erythematosus
HCQ:	hydroxychloroquine
HSV:	herpes simplex virus
IFN:	interferon
IFNAR1:	type I interferon receptor
IVIg:	intravenous immunoglobulin
MMF:	mycophenolate mofetil
MTX:	methotrexate
RTX:	rituximab
SCS:	systemic corticosteroids
SLE:	systemic lupus erythematosus
TCS:	topical corticosteroids
VTE:	venous thromboembolism
VZV:	varicella zoster virus

CASE SERIES

Six patients with CCLE treated with more than one ANI infusion were included in this case series. Patients 2 to 5 have a confirmatory skin biopsy consistent with cutaneous lupus, while patient 1 has

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Table I. Patient demographics and clinical characteristics

Patient number	Age, sex, and race	SLE	Systemic SLE features	CLE subtype	Generalized skin disease	Disease duration (y)	Current smoker	Prior systemic therapy	Concomitant therapy on ANI	Time to >90% improvement (mo)	Therapy duration (mo)	Adverse effects of ANI
1	52, female, Black	Yes	VTE, pancytopenia, nephritis, arthritis	DLE	Yes	2	No	HCQ, SCS, AZA, MMF, MTX, belimumab	HCQ, AZA	2	3	None
2	42, female, White	Yes	VTE, nephritis, lymphopenia, arthritis	CCLE	Yes	26	No	HCQ, CQ, SCS, AZA, MMF, MTX, RTX, IVIg, belimumab	HCQ, IVIg, prednisone 5 mg	2	8	None
3	37, female, White	Yes	Raynaud, anemia, arthritis	DLE	No	5	No	HCQ, CQ, SCS, MMF, MTX, dapsone, belimumab	None	3	15	HSV or VZV
4	39, male, Black	Yes	VTE, pericardial effusion, nephritis, leukopenia, arthritis	DLE	Yes	13	Yes	HCQ, CQ, SCS, AZA, MTX, CTX, IVIg, RTX, belimumab	CQ, methylpred 4 mg every other day	2	12	None
5	52, female, White	No		CCLE	Yes	5	Yes	MMF, HCQ, MTX, CSA	HCQ	1	6	None
6	66, female, White	No		DLE	No	12	No	HCQ, CQ, AZA, MMF, MTX, dapsone, belimumab	None	2	3	None

ANI, Anifrolumab; *AZA*, azathioprine; *CCLE*, chronic cutaneous lupus erythematosus; *CLE*, cutaneous lupus erythematosus; *CQ*, chloroquine; *CSA*, cyclosporine; *CTX*, cyclophosphamide; *DLE*, discoid lupus erythematosus; *HCQ*, hydroxychloroquine; *HSV*, herpes simplex virus; *IVIg*, intravenous immunoglobulin; *MMF*, mycophenolate mofetil; *MTX*, methotrexate; *RTX*, rituximab; *SCS*, systemic corticosteroids; *SLE*, systemic lupus erythematosus; *VTE*, venous thromboembolism; *VZV*, varicella zoster virus.

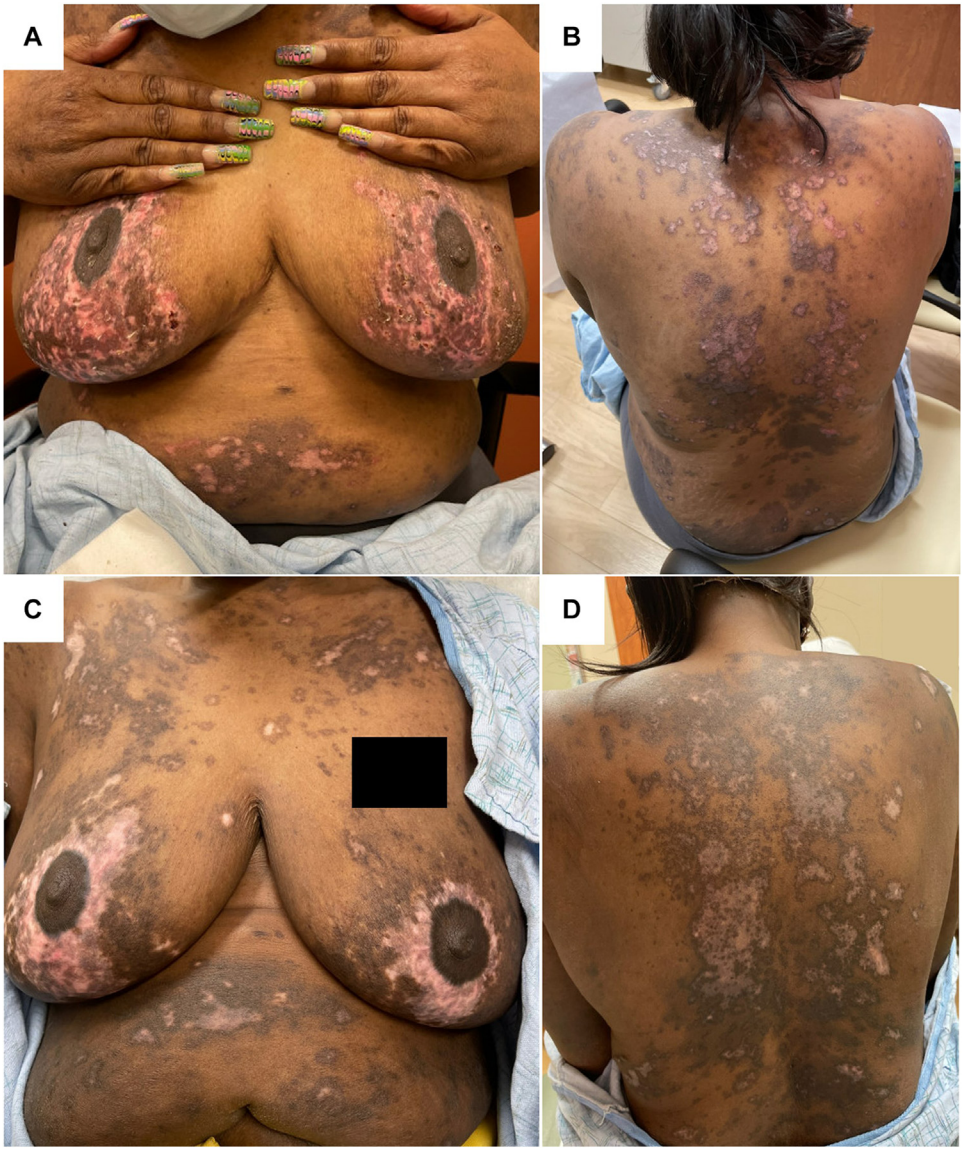

Fig 1. Widespread *pink*, scaly plaques on the chest (**A**) and back (**B**) in a patient with systemic lupus erythematosus and generalized discoid lupus erythematosus. The patient initially cleared, then flared after cessation of anifrolumab infusions. She cleared again 2 months after re-starting infusions (**C** and **D**).

not had a skin biopsy. The following patient demographics were collected: age, sex, race, diagnosis of SLE, medical history, disease onset, CLE subtype, smoking history, and prior CLE or SLE treatments. Clinical response was assessed by clinical exam, photography, and patient reported symptoms.

We treated 6 patients from 37 to 66 years of age with a mean disease duration of 10.5 years (range, 2-26 years). Four patients had discoid lupus erythematosus (DLE) and 2 patients had hypertrophic CCLE. Four patients had concurrent SLE and 5 had generalized skin disease. Prior treatments and demographic data are summarized in Table I. Adverse side effects were rare. All tolerated the infusions well with no infusion reactions. One patient suffered a limited outbreak of either herpes simplex virus or varicella zoster virus and was effectively treated with oral valacyclovir. This is a known potential adverse effect of ANI infusions and likely a side effect of treatment. Another patient experienced a worsening of known lupus nephritis after initiation of ANI. This would not be an adverse event typical of ANI, and it remains unclear if this was a direct effect of ANI or due to a general worsening of known systemic disease. Both patients have chosen to remain on ANI treatment.

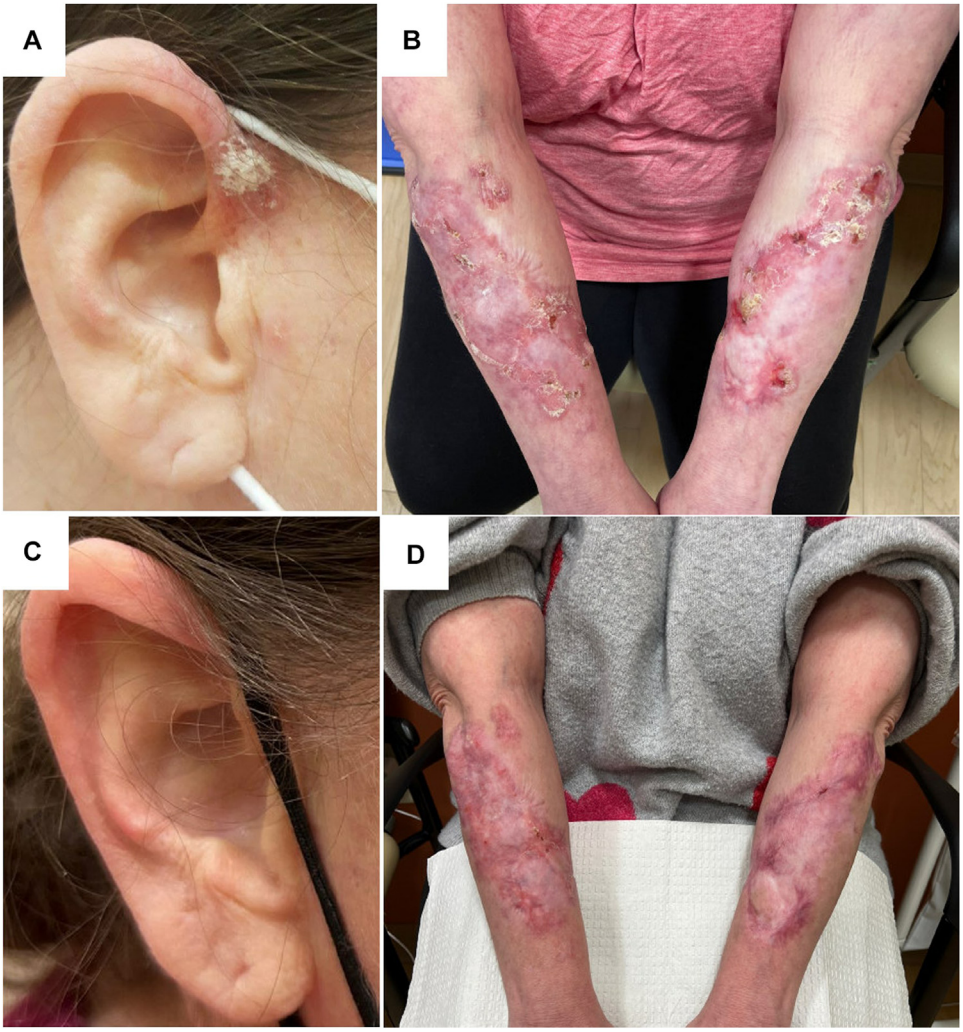

Fig 2. *Pink*, scaly hypertrophic plaques and nodules on the ears (**A**) and bilateral forearms (**B**) in a patient with hypertrophic chronic cutaneous lupus erythematosus. Marked improvement without nodularity or scale and only residual erythema and scarring 5 months after start of monthly anifrolumab infusions (**C** and **D**).

CASE PRESENTATIONS

Case 1

A 52-year-old Black female with SLE presented with recalcitrant generalized DLE of 2 years duration characterized by widespread raised, scaly, and erythematous plaques with scarring and peripheral hyperpigmentation over the face, scalp, chest (Fig 1, *A*), abdomen, back (Fig 1, *B*), and bilateral upper and lower extremities. The patient had multiple sequelae of SLE including class III lupus nephritis, pancytopenia, arthritis, and history of venous thromboembolism (VTE). She had previously failed treatment with hydroxychloroquine (HCQ), systemic corticosteroids (SCS), azathioprine (AZA), mycophenolate (MMF), methotrexate (MTX), belimumab, and high potency topical corticosteroids (TCS). After 2 infusions of ANI, the patient had an excellent skin response with near compete clearance of all active DLE lesions; she reports that ANI was life-changing and that she was able to return to work. Unfortunately, she developed worsening lupus nephritis and the decision was made to stop ANI and undergo treatment with a 12-week course of cyclophosphamide with MTX and increased SCS. Her skin disease quickly flared and worsened on this treatment regimen. After about 4 months, given stable renal disease and the patient's desperate desire to restart infusions, she was switched to ANI in conjunction with AZA (which had been ineffective for her skin disease, but potentially kidney-protective). Her skin quickly cleared within 2 months of reinitiating ANI and AZA (Fig 1, *C* and *D*) and is

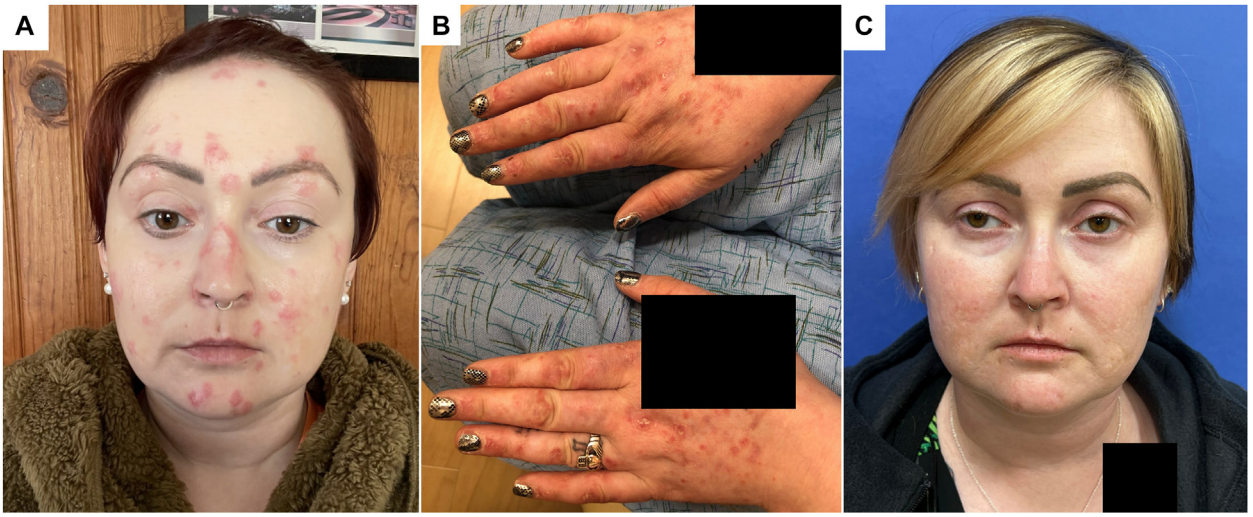

Fig 3. *Pink*, scaly papules and plaques on the face (**A**) and hands (**B**) in a patient with systemic lupus erythematosus with discoid lupus erythematosus. Three months after the start of monthly anifrolumab infusions, the patient's skin was clear of active disease (**C**).

currently off all other therapy, including TCS and SCS; her renal disease remains stable.

Case 2

A 42-year-old White female with SLE of 26 years duration with a history of renal insufficiency, VTE, arthritis, and lymphopenia presented with recalcitrant CCLE (hypertrophic subtype) of the ears (Fig 2, *A*), face, and arms. Her forearm disease was extensive (Fig 2, *B*) and complicated by frequent ulceration and recurrent squamous cell carcinomas; balancing treatment of her autoimmune and malignant diseases has been difficult. Previous treatments included HCQ, chloroquine (CQ), SCS, AZA, MMF, MTX, intravenous immunoglobulin (IVIg), belimumab, rituximab, intralesional steroid injections, and TCS under occlusion, all of which failed to adequately control her skin disease. At one point she also developed widespread reactive granulomatous dermatitis, which responded adequately to IVIg. Initiation of ANI resulted in rapid improvement of her CCLE skin disease after a few infusions, with only residual erythema and scarring with minimal scale at 5 months (Fig 2, *C* and *D*). She remains on HCQ, IVIg, and prednisone 5 mg daily, but is no longer using TCS.

Case 3

A 37-year-old White female with SLE since the age of 11 years complicated by Raynaud's syndrome, anemia, and arthritis presented with scattered pink, scaly papules and plaques on the face (Fig 3, *A*), scalp, ears, dorsal fingers, and hands (Fig 3, *B*), arms and legs consistent with generalized DLE. These lesions were refractory to treatment with TCS, HCQ, SCS, MMF, MTX, dapsone, and belimumab. After 3 cycles of ANI, the patients' skin was clear (Fig 3, *C*) and remained clear on ANI with no other therapy. At about 12 months of ANI treatment, she developed a vesicular rash on the right buttocks consistent with either herpes simplex virus or varicella zoster virus and was effectively treated with oral valacyclovir. She skipped one ANI infusion due to the outbreak and had a minimal flare of the skin disease on her dorsal hands, which quickly resolved with reinitiation of therapy.

Case 4

A 39-year-old Black male with SLE of 13 years duration complicated by class II nephritis, arthritis, leukopenia, scarring DLE, and history of VTE and pericardial effusion presented with atrophic and scaly pink papules and plaques with scarring and peripheral hyperpigmentation on the face, scalp (Fig 4, *A*), ears, chest (Fig 4, *B*), arms, hands, and feet. Previous failed treatments included TCS, SCS, HCQ, CQ, AZA, MTX, cyclophosphamide, rituximab, belimumab, and IVIg. His skin responded quickly after 2 infusions of ANI (Fig 4, *C*) with no active lesions at 10 months of continued treatment (Fig 4, *D*). He remains on CQ, is tapering SCS (currently methylprednisolone 4 mg every other day) and is no longer using topical steroids. Per recent nephrology visit, the

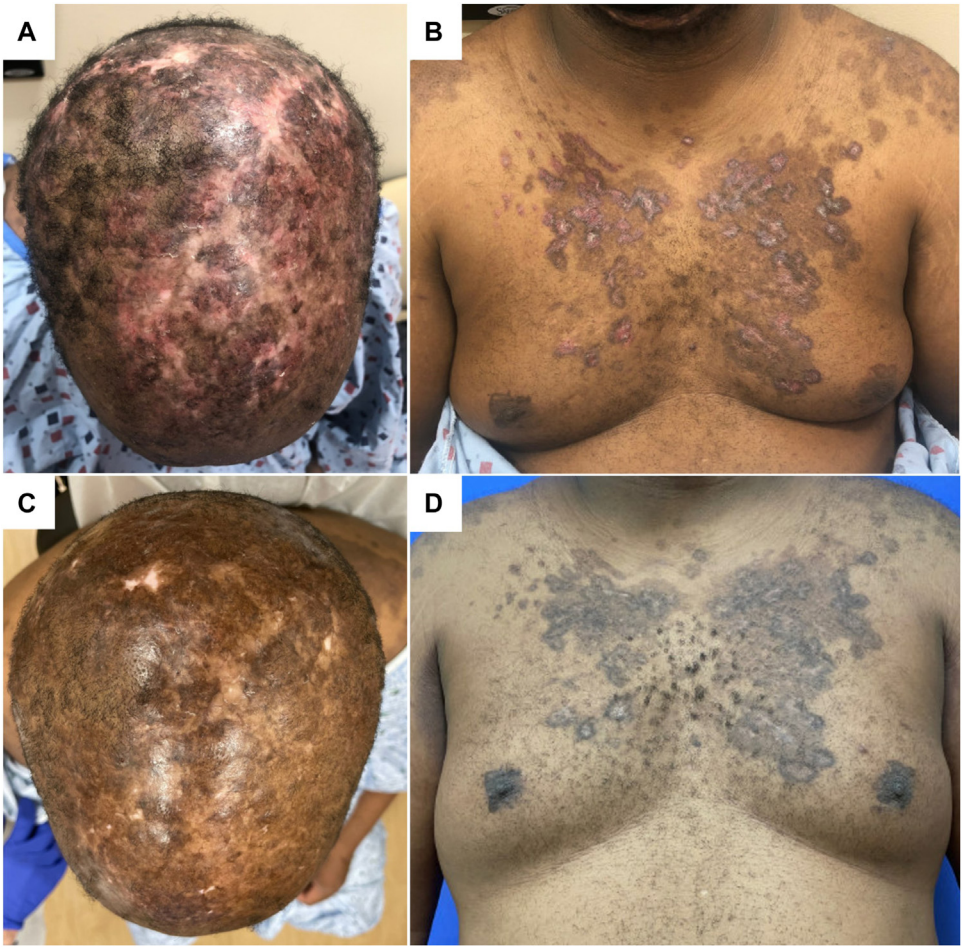

Fig 4. *Pink*, scaly plaques on the scalp (**A**) and chest (**B**) in a patient with systemic lupus erythematosus and generalized discoid lupus erythematosus 1 month before start of anifrolumab infusions. Almost complete resolution of scale and erythema noted 2 months after start of infusions (**C**), which continued at 10 months (**D**).

patient's lupus nephritis remains stable. He remains a current smoker.

Case 5

A 52-year-old White female with hypertrophic CCLE diagnosed 5 years prior presented with pruritic, pink, and hypertrophic thickened plaques on the face, scalp, neck, arms (Fig 5, *A*), chest, back (Fig 5, *B*), lower legs, and feet despite previous treatment with HCQ, MMF, MTX, and cyclosporine. The forearm lesions were the most difficult to control, with TCS under occlusion and intermittent intralesional steroid injections providing some intermittent and temporary relief. After commencement of ANI infusions, the patient reported dramatic improvement in itch and appearance of skin within 2 weeks, with resolution of active lesions with only residual scarring and post-inflammatory hyperpigmentation at 2 months (Fig 5, *C* and *D*). She remains on HCQ, but is no longer using TCS. She remains a current smoker.

Case 6

A 66-year-old White female presented with a 12-year history of red, scaly, tender plaques, and scarring alopecia of the scalp consistent with DLE (Fig 6, *A*). Previous failed treatments included intralesional steroids, TCS, HCQ, CQ, AZA, MTX, MMF, belimumab, and dapsone. After 2 infusions of ANI, her scalp disease was completely resolved with only residual scarring (Fig 6, *B*). Her CQ dose was reduced to 250 mg every other day and she is no longer using TCS.

DISCUSSION

Treatment of refractory CCLE remains challenging for a myriad of reasons. The limited

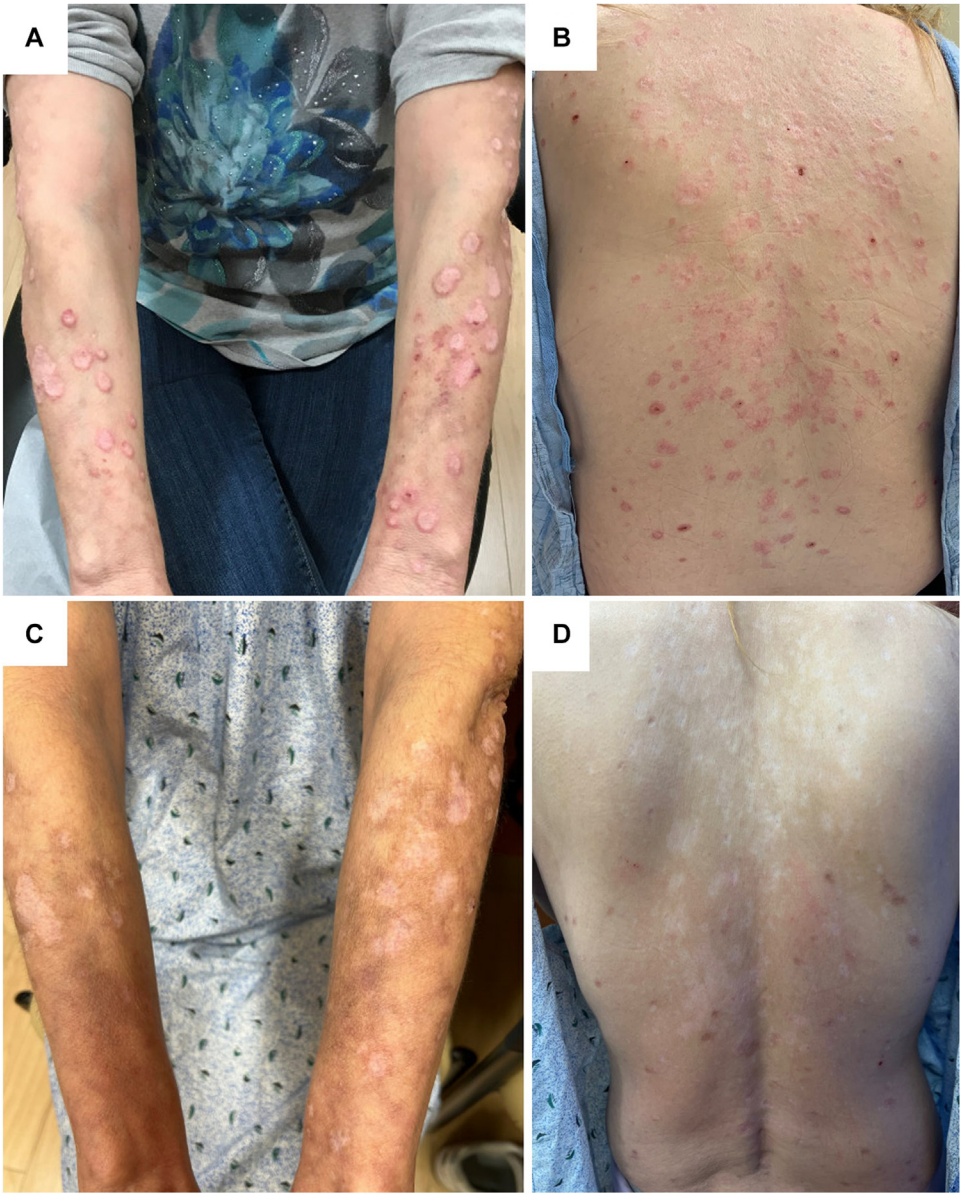

Fig 5. *Pink*, scaly hypertrophic plaques and nodules on the forearms (**A**) and back (**B**) in a patient with hypertrophic chronic cutaneous lupus erythematosus. Near total clearance of skin disease 2 months after start of anifrolumab infusions (**C** and **D**).

medications available are not always effective and many carry serious adverse effects, the most common being immunosuppression. Additionally, the chronic use of steroids, which most SLE/CLE patients are exposed to, carries significant long-term risks. Due to the visibility of skin lesions, cutaneous disease has a significant impact on patients' quality of life, comfort with socialization, and self-image.[6] Given the morbidity associated with the scarring and dyspigmentation wrought by CCLE, quick and efficacious treatment is highly desired.[5] Type I IFNs are key mediators and correlate with cutaneous disease in SLE, as well as specific CLE subtypes, subacute cutaneous, and DLE.[2,13] ANI, a fully human monoclonal antibody against IFNAR1 received Food and Drug Administration approval for SLE in 2021. All 3 major ANI trials (MUSE [Maximal Use Systemic Exposure], TULIP [Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus]-1, and TULIP-2) carried a secondary endpoint evaluating cutaneous disease

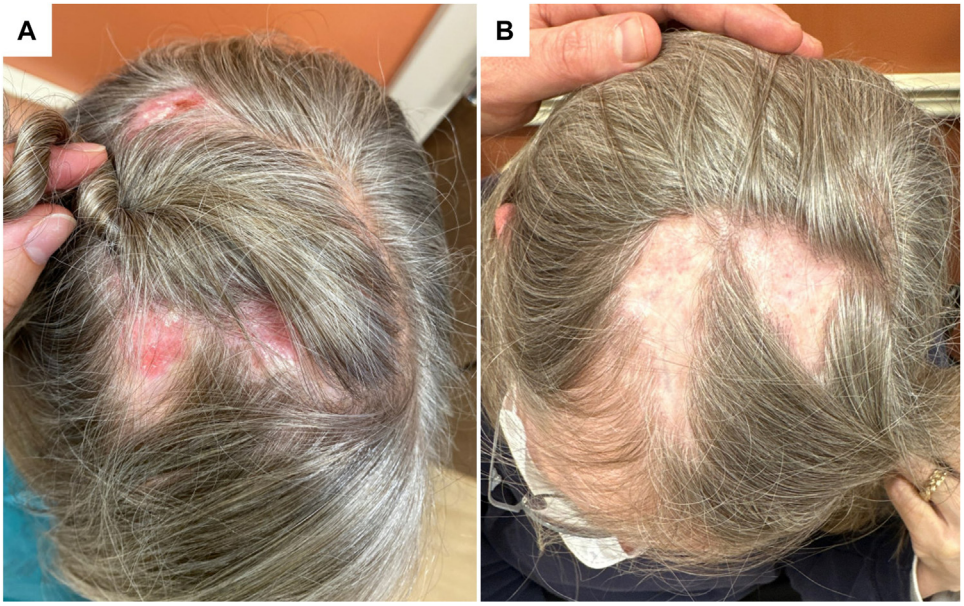

Fig 6. *Red*, scaly, tender plaques on the scalp (**A**) in a patient with discoid lupus erythematosus with complete resolution of active disease and only residual smooth scars after 2 anifrolumab infusions (**B**).

improvement as follows: patients with a Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity (CLASI-A) of 10 or greater at baseline achieving a 50% or more reduction in CLASI-A.[14] In the MUSE trial this was evaluated at week 52 with 63% of those on ANI compared to 30.8% on placebo (P = .013) achieving this endpoint. In a post hoc analysis of pooled data from TULIP-1 and TULIP-2, at week 52, 46% of patients receiving ANI compared to 25% placebo achieved this endpoint. As early as week 8, a significantly greater proportion of patients receiving ANI achieved a sustained CLASI-A response compared to placebo.[15] CLE subtypes were not categorized in these trials but given the overlapping pathophysiology of SLE and CLE it is no surprise that ANI provided clinical benefit to patients with severe cutaneous disease.

This case series of 6 patients with severe, disfiguring, recalcitrant CCLE successfully treated with ANI includes the first reported cases in a male patient and in hypertrophic CCLE (Table II). Our series adds 2 additional cases without concomitant SLE to the single previously published case.[8] Most of our subjects (5/6) had failed prior belimumab treatment, consistent with many of the reported cases, which suggests that treatment with ANI should be considered prior to belimumab for severe CCLE. All 6 patients had significant improvement, most after the first infusion and near-complete clearance of disease activity within a few months. Treatment success was not dependent on sex, race, smoking status, concomitant SLE, or CLE subtype. Of note, one patient had worsening renal disease despite clearance of severe skin disease. This suggests that ANI maybe be preferentially more effective for cutaneous disease than for lupus nephritis. More studies will be necessary to evaluate this therapeutic discrepancy. Treatment and follow-up are ongoing for all patients.

There are several limitations to this case series, which include small sample size, retrospective nature, lack of documented CLASI-A scores during clinic visits, and lack of a control group. While we, along with others, have observed therapeutic efficacy in the treatment of CCLE, further investigations to assess the efficacy and safety across the CLE spectrum are required. This case series is an addition to the limited literature on ANI use specifically for CCLE and showcases ANI's potential as a therapeutic beacon in recalcitrant CCLE.

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Conflicts of interest

None disclosed.

Table II. Summary of published literature

Reference	Subjects (*n*)	Sex (F/M)	Race/ethnicity (B/W/H)	SLE (Y/N)	CLE subtypes (s)	Smoker (Y/N)	Belimumab prior (Y/N)	Photographs (Y/N)	Assessment tools
Plüß et al[11]	1	1/0	0/1/0	1/0	SCLE	Not reported	1/0	1/0	CLASI, SLEDAI-2K
Trentin et al[8]	2	2/0	0/2/0	1/1	DLE, chilblains	Not reported	0/2	2/0	CLASI, LIT, SLEDAI-2K, Skindex-16
Blum et al[9]	3	3/0	3/0/0	3/0	DLE	2/1	2/1	3/0	
Shaw et al[10]	8	8/0	3/2/3	8/0	DLE	Not reported	4/4	1/7	CLASI
Chasset et al[12]	11	11/0	Phototype reported	11/0	DLE, SCLE, chilblains	4/7	11/0	0/11	CLASI, SLEDAI
Kowalski et al	6	5/1	2/4/0	4/2	Hypertrophic CCLE, DLE	2/4	5/1	6/0	

CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity; *CLE*, cutaneous lupus erythematosus; *DLE*, discoid lupus erythematosus; *SCLE*, subacute cutaneous lupus erythematosus; *SLEDAI*, systemic lupus erythematosus disease activity index.

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