Case series of anifrolumab for treatment of cutaneous lupus erythematosus and lupus-related mucocutaneous manifestations in patients with SLE

Aaron Bao 1, Michelle A Petri 1, Andrea Fava 2, Jun Kang 1

ABSTRACT
Objective To assess the efficacy of anifrolumab, a type-1 interferon receptor subunit-1 monoclonal antibody, in treating refractory cutaneous lupus erythematosus (CLE) and lupus non-specific mucocutaneous manifestations in patients with systemic lupus erythematosus (SLE).

Methods A case series comprising four SLE patients with refractory CLE received anifrolumab (300mg) as add-on therapy. Medical history, serological markers and images were collected. Cutaneous Lupus Erythematosus Disease Area and Severity Index–Activity (CLASI-A) was assessed at baseline and post-treatment visits.

Results Patient 1: Anifrolumab effectively treated refractory chronic cutaneous lupus erythematosus with lupus panniculitis and calcinosis cutilis. Patient 2: Anifrolumab demonstrated rapid improvement in generalised discoid lupus, achieving a substantial reduction in CLASI-A from 40 to 8. Patient 3: Switching from belimumab to anifrolumab led to notable improvement in photosensitivity and tumid lupus. Patient 4: Anifrolumab effectively managed refractory subacute cutaneous lupus erythematosus, resulting in remarkable cutaneous improvement and successful tapering of prednisone and mycophenolate mofetil.

Conclusion Anifrolumab demonstrates efficacy in treating refractory CLE subtypes and lupus non-specific mucocutaneous manifestations in SLE patients. Further studies are needed to establish response rates, optimal dosing, and long-term outcomes.

INTRODUCTION
Anifrolumab is a monoclonal antibody that binds to type-1 interferon (IFN) receptor subunit-1 and blocks the action of IFN, a key inflammatory driver in SLE and cutaneous lupus erythematosus (CLE). Anifrolumab was approved by the Food and Drug Administration (FDA) in 2021 for moderate-to-severe SLE in adults receiving standard therapy, based on the MUSE, TULIP (Treatment of Uncontrolled Lupus via the Interferon Pathway-1) and TULIP-2 trials.

RESULTS
Patient 1: generalised discoid lupus (generalised DLE), chilblain lupus (ChLE), lupus panniculitis (LPE), calcinosis cutis
Patient 2: generalised discoid lupus, achieving a substantial reduction in CLASI-A from 40 to 8. Patient 3: Switching from belimumab to anifrolumab led to notable improvement in photosensitivity and tumid lupus. Patient 4: Anifrolumab effectively managed refractory subacute cutaneous lupus erythematosus, resulting in remarkable cutaneous improvement and successful tapering of prednisone and mycophenolate mofetil.

Conclusion Anifrolumab demonstrates efficacy in treating refractory CLE subtypes and lupus non-specific mucocutaneous manifestations in SLE patients. Further studies are needed to establish response rates, optimal dosing, and long-term outcomes.


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by calcinosis cutis. Previous treatment included methotrexate (MTX) and clobetasol.

Quinacrine (QC) and intralesional/topical sodium thiosulfate partially improved her facial and chest DLE and calcinosis cutis in the extremities, but not her ChLE and LEP. Her CLASI-A increased from 15 to 19 over 1 year due to progressively worsening cutaneous symptoms, prompting anifrolumab initiation.

Five days after her first infusion, she experienced erythema and oedema of LEP plaques on her lower legs, which necessitated intramuscular triamcinolone. This reaction was presumed to be a paradoxical flare of LEP, triggered by an anifrolumab-related immunologic response to her calcinosis cutis. Additionally, her urine protein-creatinine ratio (UPCR) briefly increased from 0.23 to 0.31. Anifrolumab was temporarily discontinued, and her baseline regimen was resumed.

Four weeks after initial infusion, softening of her LEP plaques was observed. Based on this improvement, a decision was made to reintroduce anifrolumab 3 months later. Her cutaneous

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<td>Diagnosis</td>
<td>SLE, DLE, ChLE, LEP</td>
</tr>
<tr>
<td>Serology/labs</td>
<td>ANA 1:640 Anti-dsDNA Anti-RNP Anti-Smith aPL Anti-Ro/La Cryoglobulins Leucopenia ESR elevation</td>
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<td>Lupus specific manifestations and cutaneous diagnoses</td>
<td>Class II lupus nephritis Discoid lupus Lupus panniculitis Chilblain lupus Lupus alopecia</td>
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<td>Non-specific manifestations</td>
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<tr>
<td>Prior medications</td>
<td>HCQ QC MMF MTX Dipyridamole Prednisone Sodium thiosulfate Clobetasol</td>
</tr>
<tr>
<td>Current medications</td>
<td>HCQ QC MMF Prednisone Anifrolumab</td>
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<td>First anifrolumab infusion</td>
<td>10/2022 (discontinued due to lupus panniculitis) 1/2023</td>
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<td>Months to improvement</td>
<td>1 following second infusion</td>
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<td>Months to maximal improvement</td>
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CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index–Activity; CLE, cutaneous lupus erythematosus; CQ, chloroquine; H, hydroxychloroquine; LEP, lupus panniculitis; MMF, mycophenolate mofetil; MTX, methotrexate; QC, quinacrine; SCLE, subacute cutaneous lupus erythematosus; TLE, tumid lupus erythematosus.

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<td>SLE, TLE</td>
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<td>ANA 1:640 Anti-dsDNA Anti-RNP Anti-Smith aPL Anti-Ro/La Low C3/C4 Lymphopenia Proteinuria</td>
<td>ANA 1:320 Anti-dsDNA aPL Anti-Ro60 Anti-thyroglobulin Low C3/C4 Leucopenia Thrombocytopenia</td>
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<td>Lupus specific manifestations and cutaneous diagnoses</td>
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<td>Class V lupus nephritis Discoid lupus</td>
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<td>Non-specific manifestations</td>
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<td>Arthralgia Upper palate ulceration</td>
<td>Poikiloderma Oral ulceration Photosensitivity</td>
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<tr>
<td>Prior medications</td>
<td>HCQ QC MMF MTX Dipyridamole Prednisone Sodium thiosulfate Clobetasol</td>
<td>HCQ MMF Prednisone Dapsone Azathioprine Tacrolimus IM triamcinolone</td>
<td>HCQ Belimumab Desonide Tacrolimus IM triamcinolone</td>
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Due to her severe mucocutaneous disease, anifrolumab was initiated. Two months after starting therapy, she had remarkable improvement, corresponding to CLASI-A of 8 (figure 1). However, she reported persistent myalgia and malaise after each infusion. Additionally, a week after her first infusion, repeat SLE labs revealed worsening proteinuria, subsequently confirmed to be class V LN. MMF was added to her treatment in the context of her DLE and LN.

Three months after anifrolumab initiation (1 month after starting MMF), her UPCR improved from 1.27 to 0.23, and prednisone was tapered from 5 to 0.5 mg. Despite improvements, her fourth anifrolumab infusion was halted due to patient’s concern regarding immunosuppression following an upper respiratory infection that required moxifloxacin.

**Patient 3: photosensitivity and tumid lupus erythematosus (TLE)**

Patient 3 is a 55-year-old female with Fitzpatrick skin-type I with SLE based on oral ulcers, ANA 1:320, anti-dsDNA, antiphospholipid antibodies, leucopenia, thrombocytopenia, low C3/C4 and supported by anti-Ro60. She was referred to dermatology for persistent photosensitivity and recurrent facial rash. Her history and examination were consistent with TLE.

Despite 16 months of belimumab and HCQ treatment, she continued to exhibit debilitating cutaneous symptoms leading to decreased quality of life, and a decision was made to switch belimumab to anifrolumab. Although the episodic flares associated with sun exposure did not allow for accurate assessments of her mucocutaneous disease using CLASI-A, the patient reported reduced photosensitivity and decreased frequency/severity of TLE flares at 3 month follow-up. Her CLASI-A decreased from 3 to 0 based on improvements of her oral ulcers and hair loss.

**Patient 4: subacute cutaneous lupus erythematosus (SCLE)**

Patient 4 is a 58-year-old male with Fitzpatrick skin-type II and SLE based on SCLE, leucopenia, thrombocytopenia, ANA 1:80, antiphospholipid antibodies and supported by anti-histone antibodies, anti-Ro60 with an active smoking history. He was referred to dermatology for refractory SCLE, initially triggered by trimethoprim-sulfamethoxazole, affecting his neck, torso and extremities. His SCLE remained active with CLASI-A 15 despite undergoing treatment with HCQ 400 mg, MMF 3 g/day, prednisone 15 mg, dapsone 50 mg and topical triamcinolone. Blood HCQ level >1000 ng/mL was consistent with medication compliance. A trial of chloroquine (CQ) 250 mg and dapsone 100 mg did not improve his SCLE, and he continued to require prednisone bursts, ranging from 15 to 30 mg, that adversely affected control of his type 2 diabetes mellitus and hypertension. Thorough review of his medication list did not suggest drug-induced SCLE. Consequently, anifrolumab was initiated. There was an unexplained improvement in his disease (CLASI-A 5) just before starting anifrolumab, which was...
Patient 1, who had refractory CCLE complicated by calcinosis cutis, was resistant to multiple therapies over 17 years. Three months after her initial anifrolumab infusion and subsequent LEP flare, her second infusion led to complete remission of DLE, near-complete remission of ChLE, partial remission of LEP and resolution of superficial calcinosis cutis—conditions historically resistant to conventional therapies. It is unclear if suspected deep calcinosis cutis associated with LEP have resolved based on visual examination. Patient 2, presenting with highly active generalised DLE and LN, exhibited rapid improvement in mucocutaneous and renal manifestations within 1 month of anifrolumab treatment. The potential benefits of anifrolumab in LN were demonstrated in the TULIP-LN1 trial, showing increased renal remission rates and sustained reduction in glucocorticoid dosage.

Patient 3, who had TLE and photosensitivity, showed minimal response to HCQ and belimumab but notable improvements in cutaneous symptoms after switching belimumab to anifrolumab. Patient 4 initially demonstrated some improvement before starting therapy but still required prednisone 10 mg. Nevertheless, anifrolumab facilitated continued progress, enabling rapid taper of prednisone and MMF, leading to sustained remission of his SCLE.

For these patients, an important clinical decision was whether to initiate treatment with belimumab or anifrolumab. Belimumab is FDA approved to treat active LN. In a phase II trial of anifrolumab in patients with active LN, the primary endpoint was not met despite anifrolumab intensified regimen showing numerical improvements over placebo in other endpoints. While belimumab has also demonstrated promise in treating CLE, it has a slower onset of action, typically taking around 20 weeks to achieve maximal effects. In contrast, in the author’s (JK) experience, anifrolumab displays a more rapid and robust improvement in refractory CLE. Consequently, when cutaneous manifestations predominated, as in patients 1 (with well-managed LN using MMF) and 4 (without renal involvement), anifrolumab was preferred. For patient 2, her first infusion of anifrolumab preceded LN diagnosis, and MMF was preferred due to skin involvement and proteinuria.

While existing literature on anifrolumab for CLE has predominantly focused on DLE, with limited reports on SCLE and ChLE, this case series contributes to the growing body of evidence supporting the versatility and effectiveness of anifrolumab across different treatment-refractory CLE subtypes. To our knowledge, this case series provides the first reported description of anifrolumab use in TLE/photosensitivity (patient 3), superficial calcinosis cutis and LEP (patient 1). Furthermore, we offer comprehensive clinical insights on potential side effects and treatment efficacy. While larger studies are necessary to establish response rates, optimal dosing and long-term outcomes, targeting IFN-signalling represents a significant advancement in managing refractory CLE and...
other lupus non-specific dermatologic manifestations, improving disease control and alleviating symptoms.

Twitter Andrea Fava @andreafava

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Contributors The authors confirm contribution to the paper as follows: study conception and design: AB, JK; data collection: AB, MAP, AF, JK; analysis and interpretation of results: AB, MAP, AF, JK; draft manuscript preparation: AB, MAP, AF, JK. All authors reviewed the results and approved the final version of the manuscript.

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Competing interests None declared.

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Ethics approval The study has been approved by the Johns Hopkins Medicine Institutional Review Board (IRB). The approval ensures that the study adheres to rigorous ethical and safety standards, protecting the rights and well-being of all participants involved. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to containing information that could compromise the privacy of research participants.

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ORCID iDs
Aaron Bao http://orcid.org/0000-0002-2069-9985
Michelle A Petri http://orcid.org/0000-0003-1441-5373
Andrea Fava http://orcid.org/0000-0001-6738-4836

REFERENCES