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CASE REPORT

Anifrolumab in Refractory Oral Manifestations in Systemic Lupus Erythematosus: A Case Report and Literature Review

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Abstract: Oral manifestations are a frequent yet underrecognized feature of systemic lupus erythematosus (SLE), contributing substantially to patient morbidity and reduced quality of life. They are insufficiently represented in clinical outcome measures and therapeutic guidelines, despite their clinical relevance. We report the case of a 39-year-old woman with SLE who developed severe, refractory tongue ulcers and glossodynia persisting for three years, unresponsive to hydroxychloroquine (HCQ), azathioprine (AZA), colchicine, methotrexate (MTX), and glucocorticoids (GC). Belimumab was discontinued due to gastrointestinal intolerance and lack of efficacy on oral lesions. The patient was subsequently treated with anifrolumab 300 mg intravenously every four weeks. After the first infusion, oral ulcers resolved, arthritis improved, and corticosteroids were discontinued. Within three months, the tongue lesions had completely healed, enabling unrestricted oral intake and full resumption of professional activities. Clinical remission was maintained on anifrolumab and hydroxychloroquine alone at four months of follow-up. This case highlights the therapeutic challenge of refractory oral lesions in SLE, a manifestation not adequately addressed in current EULAR (2023 update) or ACR (2025) guidelines. While conventional immunosuppressants such as azathioprine, methotrexate, and mycophenolate mofetil remain options, their efficacy for isolated oral lesions is limited. Emerging evidence, including case reports and small series, suggests that anifrolumab may provide significant benefit for mucosal involvement. The key learning point is that refractory tongue involvement may represent a dominant and treatment-resistant manifestation of SLE, yet it can respond to targeted biologic therapy such as anifrolumab and our report adds to this growing body of evidence. Prospective comparative studies and registry analyses are required to define anifrolumab's effectiveness specifically for refractory oral manifestations and to compare outcomes with other biologics.

Keywords: systemic lupus erythematosus, oral lesions, biological therapy, anifrolumab, treatment outcome

Introduction

Oral manifestations are a frequent yet often underrecognized feature of systemic lupus erythematosus (SLE). Despite their clinical relevance, they are not consistently addressed in patient-reported outcome measures, treatment response criteria, or quality-of-life assessments, and are captured only indirectly within disease activity instruments such as the British Isles Lupus Assessment Group (BILAG) index.[1–4] Among these manifestations, oral mucosal lesions are particularly characteristic but frequently underestimated. Systematic reviews and multicenter studies indicate that the prevalence of oral lesions in SLE ranges from 20% to 40%, with some cohorts reporting rates as high as 61%.[5,6]

The most common lesions are oral ulcers, which may present as painful, erosive, or atrophic defects and can significantly impair daily activities and quality of life. In addition to ulcerations, patients with SLE may experience xerostomia due to hyposalivation, glossodynia, mucosal pigmentation, cheilitis, and periodontal involvement. These symptoms not only compromise nutrition and social interaction, but may also serve as early indicators of disease activity.[7] Diagnostic challenges arise because oral manifestations of SLE can mimic other conditions such as oral lichen

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planus, candidiasis, or neoplasms. Clinically, such lesions are relevant not only for their association with infectious complications and impaired quality of life, but also for their potential link to an increased risk of oral malignancy.[6]

Despite their importance, standardized strategies for diagnosing and managing SLE-related oral manifestations are lacking. This gap highlights the need for interdisciplinary collaboration between rheumatologists and dental specialists, and for incorporating routine oral monitoring into the comprehensive care of patients with SLE. Refractory oral ulcers, in particular, represent a therapeutic challenge. The few published case reports suggest that anifrolumab, a monoclonal antibody targeting the type I interferon receptor, may ameliorate oral disease burden, but data are sparse.[8,9] Here, we describe a patient with SLE and treatment-resistant oral ulcers who was successfully managed with anifrolumab. We also provide a literature review of current evidence on this emerging therapeutic approach.

Case Report

A 39-year-old woman with SLE presented in September 2024 with painful oral and tongue ulcers, glossodynia, fissured tongue, polyarthralgia, polymyalgia, and fatigue.

Her symptoms started in 2022 with recurrent episodes of oral ulcers, Raynaud's syndrome, polyarthralgia affecting the knees, hips, and hands, malar and V-area erythema, photosensitivity, and fatigue. Based on clinical features and blood test findings of positive ANA (1:500) and anti-Smith antibodies, she was diagnosed with SLE according to the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria.[10] She was also positive for SS-B and RNP antibodies and negative for anti-dsDNA.

She had a strong family history of autoimmune diseases: her mother had SLE, her sister dermatomyositis, and her cousin antiphospholipid syndrome.

Her medical history included mild bronchial asthma in off-drug remission, irritable bowel syndrome (IBS), and migraine managed with topiramate 50 mg daily and erenumab 70 mg once monthly.

After diagnosis in 2022, she started HCQ 5 mg/kg and azathioprine 50 mg BID, which resulted in complete resolution of cutaneous manifestations, and mild reduction in joint pain and fatigue. However, she did not get any improvement with the oral lesions after been 1.5 years on HCQ, for this reason colchicine 0.5 mg BID was prescribed in December 2023.

At follow-up in September 2024, she reported worsening of the oral symptoms and new inflammatory arthritis. Clinical examination showed six mouth ulcers; an enlarged, inflamed, and painful fissured tongue with three ulcers (Figure 1); and twelve tender and nine swollen joints, including the right knee, left wrist, and MCP and PIP joints

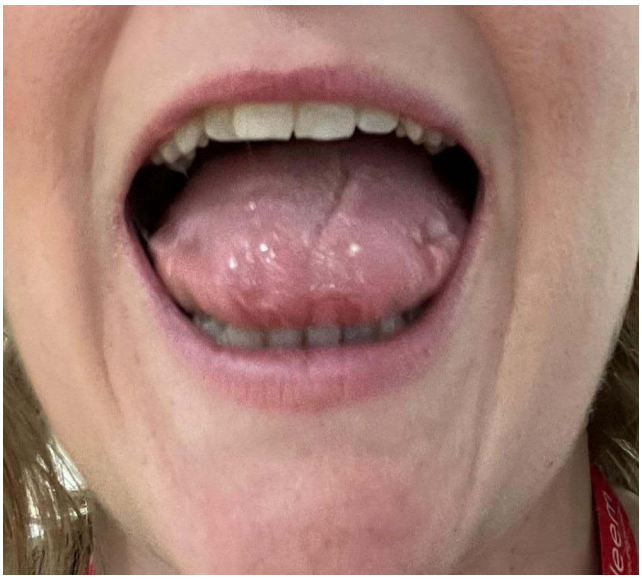

Figure 1 Fissured tongue with ulcers in September 2024 before belimumab initiation (while on azathioprine 50 mg Bid, colchicine 0.5 mg BID, and methylprednisolone 8 mg/day).

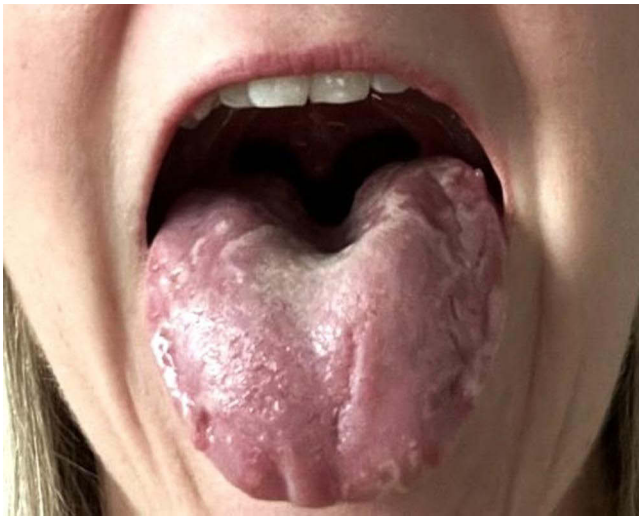

Figure 2 Worsening of fissured tongue and glossodynia one month after starting belimumab.

bilaterally. She also complained of fatigue and muscle pain. Her daily and professional life were significantly impaired: as a teacher, painful tongue ulcers and glossodynia forced her to reduce working hours, and by the end of the day she was often unable to speak. She also restricted her diet to avoid mucosal irritation. These problems contributed to depression, absenteeism, and social isolation.

Laboratory data at that time were unremarkable except for slightly elevated creatinine.

She was started on methylprednisolone 8 mg/day and MTX 15 mg/week. Three weeks after initiation, she developed an IBS flare with abdominal pain and diarrhea. Oral ulcers and arthritis improved significantly with methylprednisolone, but treatment was discontinued after 3 months because of recurrent hemorrhoidal bleeding and worsening IBS.

Thus, three years after SLE diagnosis, she had shown intolerance to MTX and GC, no response to AZA and colchicine, and only mild, temporary improvement in oral ulcers and arthritis with GC. Her SLEDAI-2K score at the last visit was 10. In accordance with the 2023 EULAR recommendations,[11] she was started on belimumab 200 mg SC weekly. After four weeks, fatigue and arthritis resolved, but oral manifestations persisted (Figure 2). She also developed worsening IBS with vomiting and diarrhea, and belimumab was discontinued.

In March 2025, she was initiated on anifrolumab 300 mg IV combined with methylprednisolone 8 mg/day. Following the first infusion, she experienced only mild transient nausea with one episode of vomiting. Since then, no adverse effects occurred. Oral ulcers resolved after the first infusion, and arthritis also improved.

After the second infusion, she had no tender or swollen joints, no fatigue, no mouth ulcers, and improvement in glossodynia and fissured tongue (Figure 3). Colchicine and methylprednisolone were discontinued after the first infusion without tapering.

After the third infusion, her tongue normalized completely, and she was able to eat without restrictions, including spicy foods. She returned to her full working schedule.

After the fourth infusion, she had no clinical or laboratory abnormalities (Figure 4). Her serum creatinine decreased to 0.96 mg/dL (previously mildly elevated at 1.08–1.10 mg/dL since March 2022), with a corresponding improvement in eGFR from 66–67 mL/min/1.73 m^2 to a normal range. Four months after starting anifrolumab, in combination with hydroxychloroquine alone, she achieved complete remission, maintained at 3-month follow-up. She also discontinued erenumab because after starting Anifrolumab her migraine is very well controlled only on topiramate.

Discussion

Although this case might initially appear straightforward because of mild disease activity, we consider it difficult-to-treat. There are currently no guideline-based treatment recommendations for oral SLE manifestations, and evidence regarding therapeutic efficacy is limited. Over three years, the patient experienced severe, persistent tongue inflammation and oral

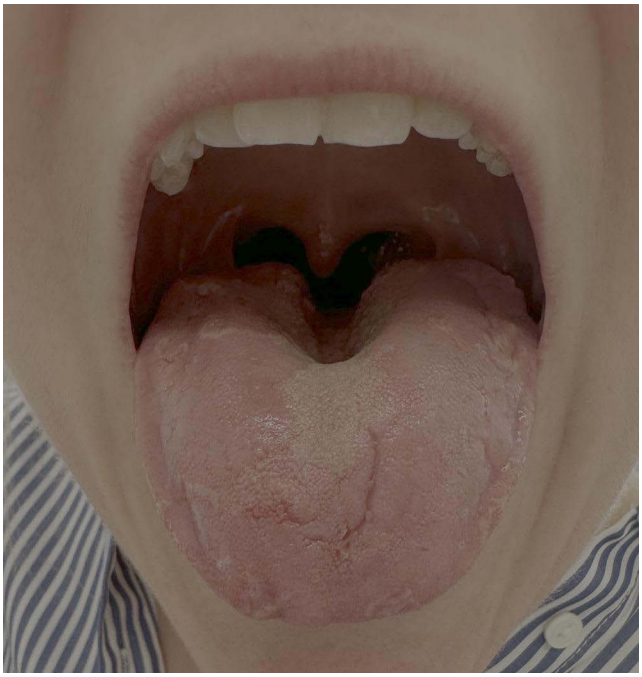

Figure 3 One month after the first anifrolumab infusion (April 2025): significant improvement with no ulcers, only residual fissuring.

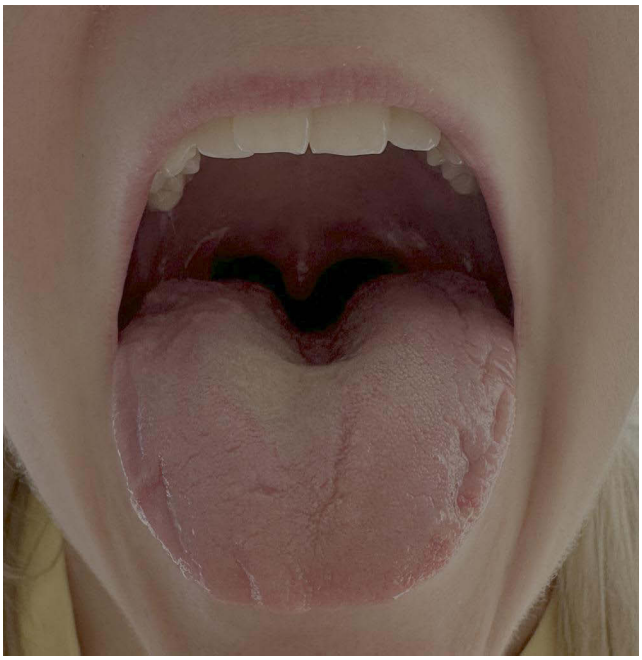

Figure 4 Three months after anifrolumab initiation (June 2025): complete resolution of refractory tongue ulcers and inflammation.

ulcers refractory to conventional therapies, with a significant impact on her professional and social life. This represents a case of disability without life-threatening or organ-threatening disease.

In the 2025 ACR guideline for SLE treatment, oral manifestations are not mentioned in the cutaneous/mucocutaneous section, which only addresses cutaneous and bullous lupus, chilblain lupus, and leukocytoclastic vasculitis.[12] Similarly, the 2023 EULAR recommendations stratify treatment by disease activity but do not specifically include oral lesions.[11]

Only the British Society for Rheumatology guidelines mention mouth ulcers in the definition of mild disease activity, recommending treatment with GC, HCQ, and MTX.[13]

Evidence for the efficacy of new biologics, anifrolumab and belimumab, in mucosal manifestations of SLE is lacking, despite their established role in cutaneous lupus. This neglect likely stems from the misconception that oral lesions are uncommon or clinically insignificant.

Currently, only a limited number of publications address this topic, with very few dedicated studies.[5–9] Compared to other SLE manifestations, clinical trial data, and registry studies, research on oral lesions remains scarce.

Table 1 summarizes the findings of three key review studies focusing on oral manifestations in patients with SLE.

Tongue involvement in SLE is relatively common; however, its clinical morphology is varied and often asymptomatic Table 2 presents the main types of lesions and their reported clinical characteristics.

An important clinical consideration is that oral lesions in patients with SLE may result not only from the disease itself but also as adverse effects of immunosuppressive therapy Specifically, methotrexate, mycophenolate mofetil, azathioprine, and cyclophosphamide are associated in their prescribing information and pharmacovigilance reports with the potential development of stomatitis, glossitis, and oral ulcers as dose-dependent adverse effects[15–18] Oral ulcers during methotrexate therapy are even considered a classic early marker of toxicity, particularly in patients not receiving folic acid supplementation[15] For azathioprine, mucosal lesions may be the first sign of severe toxicity in patients with TPMT

Table 1 Oral Manifestations in Systemic Lupus Erythematosus: Evidence from Contemporary Studies

Source	Main Oral Manifestations	Prevalence	Clinical Significance
Pérez-Piñas et al, 2020[4]	Oral ulcers, xerostomia, tongue pain/burning, mucosal pigmentation, cheilitis, periodontal lesions	Oral lesions in 20–40% (occasionally up to 75%) of patients; ulcers in ~30%	Significant reduction in quality of life, impaired nutrition, association with SLE activity
Cornet et al, 2021[3] (survey of 4375 patients in Europe)	Fatigue, joint pain, photosensitivity, as well as complaints of xerostomia, recurrent ulcers, and dental complications	Dry mouth and dental symptoms in 40% of patients	Impaired quality of life, need for multidisciplinary care (rheumatologist + dentist)
García-Ríos et al, 2022[6]	Oral ulcers (mainly hard palate), hyposalivation (up to 75%), antimalarial-induced hyperpigmentation, glossodynia, cheilitis, Sjögren's syndrome, periodontitis	14 studies on oral SLE manifestations analyzed: oral ulcers seen in 79%; glossodynia, fissured tongue, cheilitis reported in 7%; altered salivary flow in 29%; periodontitis commonly reported	SLE activity marker, diagnostic challenges (differential diagnosis with lichen planus, candidiasis, tumors); risk of worse prognosis

Table 2 Clinical Characteristics of Tongue Lesions in SLE

Type of Tongue Lesion	Clinical Characteristics	Source
Tongue ulcers	Often on the dorsal or lateral surfaces of the tongue; may be superficial or deeper, sometimes painless	Du F et al, 2023;[5] García-Ríos et al, 2022[6]
Glossodynia	Sensation of burning or pain without visible ulcers; may accompany other mucosal lesions	García-Ríos et al, 2022[6]
Cleft tongue	Specific morphology: grooves, fissuring of the tongue surface, sometimes with scarring	García-Ríos et al, 2022[6]
Atrophic areas	Areas of epithelial thinning with loss of lingual papillae, sometimes accompanied by erythema	Saeed et al, 2021[14]
Patches	White or red spots, usually asymptomatic; reported as the most frequent manifestation (53%) in an Egyptian cohort	Saeed et al, 2021[14]
Asymptomatic lesions	Approximately 77% of oral (including tongue) lesions are asymptomatic and incidentally detected	Saeed et al, 2021;[14] Du et al, 2023[5]

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or NUDT15 deficiency.[16] Mycophenolate and cyclophosphamide can induce mucositis and ulcers due to their cytostatic effects on rapidly proliferating mucosal cells.[17,18]

In contrast, glucocorticoids (eg., prednisolone) do not directly cause ulcers but, through immunosuppression, increase the risk of opportunistic mucosal infections such as candidiasis or herpetic lesions.[19] Hydroxychloroquine may rarely cause mucosal hyperpigmentation, but reports of oral ulcers as an adverse effect are virtually nonexistent.[20]

Therefore, when interpreting oral ulcers in patients with SLE, it is essential to consider not only disease activity but also the potential contribution of drug-induced toxicity.

In this context, analyzing the effectiveness of different therapeutic strategies for controlling oral ulcers is particularly relevant. Clinical data indicate that the use of antimalarials, immunomodulators, and novel biologic agents can reduce relapse frequency, shorten lesion duration, and improve patient comfort. Summarized results of these studies are presented in the tables, allowing comparison of existing approaches and outlining prospects for their further application.

Biological Therapy in Systemic Lupus Erythematosus (SLE) and Its Impact on Oral Manifestations

Belimumab is the first biologic agent approved for the treatment of SLE, targeting BAFF/BLyS. Its efficacy has been demonstrated in the BLISS-52 and BLISS-76 trials, conducted by Navarra et al[21] and Furie et al,[22] respectively. Although oral ulcers were not primary endpoints in these studies, they were included in the mucocutaneous domain of the BILAG/SLEDAI indices. Both trials reported a reduction in mucocutaneous manifestations, including oral lesions. Additionally, the BLISS-LN study by Navarra et al[21] demonstrated decreased overall disease activity and steroid-sparing effects, indirectly reducing the frequency of mucosal flare-ups.

Rituximab, although not approved for SLE treatment, remains an off-label option in refractory cases. The EXPLORER[23] and LUNAR[24] randomized controlled trials did not confirm superiority of rituximab over placebo in primary composite endpoints. However, some retrospective analyses[25,26] have shown its efficacy in patients with refractory mucocutaneous manifestations, including oral ulcers and erosions, particularly in cases of discoid or chronic mucosal involvement.

Traditional Therapy for Oral Ulcers in SLE

Hydroxychloroquine is recommended as a background treatment for all patients with SLE.[27,28] It reduces the frequency and severity of mucocutaneous manifestations, including oral ulcers, with the greatest benefit observed in the prevention of flares. Prednisolone provides rapid resolution of active ulcers, but its effect is temporary, making it unsuitable for long-term maintenance of remission.[27,29]

MTX is an alternative systemic therapy for patients with antimalarial-refractory cutaneous lupus erythematosus (CLE), particularly for those with persistent skin manifestations.[30] While it is effective for cutaneous lesions, its efficacy for oral ulcers has not been specifically established. Notably, MTX can induce oral ulcers as an adverse effect in some patients.[31,32]

Mycophenolate mofetil is used as third-line therapy for refractory cutaneous and mucosal lesions. A retrospective study by Gammon et al[33] demonstrated improvement in CLASI scores and a reduction in the recurrence of oral ulcers after 2–3 months of treatment.

AZA may be employed in patients with systemic SLE activity, although evidence for its efficacy in isolated oral lesions is limited.[17,29]

Cyclophosphamide is generally reserved for organ-threatening SLE rather than isolated mucosal lesions. Its effect on oral or mucosal ulcers is indirect, resulting from overall suppression of inflammation, but its potential toxicity makes it unsuitable for limited disease manifestations.[27]

Current guidelines for cutaneous and mucocutaneous disease preferentially cite MTX, mycophenolate mofetil or mycophenolic acid analogues, anifrolumab, and belimumab as second-line options.[11] The 2025 ACR Guideline Summary likewise recommends methotrexate, mycophenolate mofetil or mycophenolic acid analogues, anifrolumab, and belimumab for moderate-to-severe cutaneous lupus refractory to topical or antimalarial therapy. In contrast, AZA is discussed in

the context of other organ manifestations (eg., thrombocytopenia, vasculitis, arthritis) but is not highlighted as a primary treatment for cutaneous or mucocutaneous involvement.[12]

Overall, the management of oral manifestations in SLE requires a comprehensive approach. Biologic agents, particularly anifrolumab[34,35] and belimumab,[36] have demonstrated reductions in the frequency and severity of mucosal involvement when combined with standard therapy. Traditional immunosuppressants remain essential options for patients with milder or refractory manifestations, but their use must be individualized and requires careful safety monitoring.

While belimumab remains the most widely studied biologic in SLE, anifrolumab has been evaluated in multiple large trials and long-term studies, particularly for interferon-targeted therapy, demonstrating efficacy in mucocutaneous manifestations. The growing body of evidence highlights its potential to reduce the frequency and severity of oral lesions while improving systemic disease control. Findings now extend from early clinical observations to large randomized trials, with consistent benefits observed across mucocutaneous and systemic domains. Long-term extension studies[37,38] and real-world external control analyses[39] further support its role in limiting disease activity and reducing reliance on conventional immunosuppressive therapy. A comparative overview of these key clinical investigations is provided in Table 3.

These clinical effects are mechanistically coherent with the central role of type I interferon signaling in SLE pathogenesis, given that anifrolumab blocks the type I interferon receptor. Type I interferons (IFN-I) play a pivotal role in disease development and are strongly associated with specific clinical phenotypes.[42] High serum IFN activity has

Table 3 Evolution of the Evidence for Anifrolumab

Clinical Trial	TULIP-1 (2019)[40]	TULIP-2 (2019)[41]	TULIP-LTE (2022)[37]	TULIP-LTE (2025)[38]	RW Control (2025)[39]
Design	Phase III, DBPC; 123 centers in 18 countries	Phase III, DBPC; 119 centers in 16 countries	3-year LTE; DBPC; 547 patients	3-year LTE with treat-to-target analysis; 369 patients	Anifrolumab (354 patients from TULIP) vs. external RW controls (561 from TLC cohort)
Number of patients	457 patients (anti-IFN: 150 mg n=93; 300 mg n=180; placebo n=184)	362 patients (anti-IFN 300 mg, n=180; placebo, n=182)	547 patients: 257 continued 300 mg; 67 switched from 150 mg; 223 from placebo rerandomized to 300 mg or placebo	369 patients (anti-IFN 300 mg, n=257; placebo, n=112)	354 patients in the anifrolumab group vs. 561 in real-world SOC
Primary endpoint	SRI-4 at week 52	BICLA at week 52	Safety and tolerability (SAEs, infections, discontinuations)	LLDAS and DORIS (achievement and time in state over 4 years)	Change in SDI over 208 weeks; time to progression
Results	SRI-4 not achieved (36% vs. 40%); but signals of benefit in BICLA, CLASI, steroid-sparing	BICLA achieved (47.8% vs. 31.5%; p=0.01); efficacy and safety confirmed	Safety: SAEs 8.5 vs. 11.2/100 patient-years; serious infections 3.7 vs. 3.6; steroid-sparing; sustained reduction in SLEDAI-2K	LLDAS: 36.9% vs. 17.1% (OR 2.7; p=0.0081); DORIS: 30.3% vs. 18.3% (OR 1.9; p=0.0663); more time off GC/IS	Mean SDI increase: 0.162 vs. 0.587 (p<0.001); 59.9% reduced risk of SDI progression (HR 0.40; p=0.005)
Conclusion	Efficacy signals observed, but not confirmed by SRI-4; need for repeat trial	Efficacy confirmed (BICLA) and acceptable safety; basis for approval	Stable safety profile over 4 years; steroid-sparing; sustained activity reduction, even during the COVID-19 pandemic	Long-term efficacy confirmed in treat-to-target context (LLDAS, DORIS); strategic benefit of anifrolumab	Anifrolumab reduces rate of organ damage accumulation; potentially disease-modifying therapy

Abbreviations: BICLA, British Isles lupus assessment group-based composite lupus assessment; CLASI, cutaneous lupus erythematosus disease area and severity index; DBPC, double blind, placebo controlled; DORIS, definition of remission in systemic lupus erythematosus; GC, glucocorticoids; HR, hazard ratio; IFN, interferon; IS, immunosuppressives; LLDAS, lupus low disease activity state; LTE, long-term extension; OR, odds ratio; RW, real-world; SOC, standard of care; SAE, serious adverse event; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index; SLEDAI-2K, systemic lupus erythematosus disease activity index 2000; SRI-4, systemic lupus erythematosus responder index 4; TLC, Toronto Lupus Clinic; TULIP, therapeutic use of lymphocyte inhibitor product.

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been consistently linked to constitutional, hematologic, and mucocutaneous manifestations, including oral lesions. In treatment-naïve SLE patients, elevated IFN activity correlates with baseline disease activity (SLEDAI-2K), mucocutaneous involvement, and treatment response. Distinct IFN signatures further stratify clinical expression, with increased IFN-α levels particularly associated with active mucocutaneous inflammation and anti-Ro60 positivity. These data support a plausible pathophysiological link between systemic IFN-I activation and persistent oral mucosal disease in SLE, reflecting immune-mediated epithelial injury and amplified local inflammation.[43,44]

Chronic oral lesions in SLE require careful differential diagnosis, including aphthous stomatitis, erosive lichen planus, drug-induced mucositis, viral infections (eg., herpes simplex virus), Behçet disease, and traumatic lesions; attribution to lupus should rely on systemic context, serology, and, when required, histopathology. In this case, dental specialist evaluation confirmed SLE-related oral involvement, underscoring the importance of interdisciplinary collaboration. Importantly, from the patient's perspective, the achieved clinical outcome fully met her expectations.

Limitations and Future Directions

The present report describes a single patient and therefore cannot establish generalizable conclusions. No validated oral disease severity score was applied, which limits objective quantification of mucosal involvement. Follow-up duration was relatively short, and longer observation is needed to assess durability of response and relapse risk. Although the rapid improvement after anifrolumab suggests therapeutic efficacy, a contributory effect of concomitant corticosteroids cannot be fully excluded. Histopathological confirmation was not obtained, consistent with current clinical practice where biopsy is not routinely required in typical mucocutaneous SLE lesions and when clinical diagnosis is clear. Nevertheless, together with emerging case reports and small series, these findings support the rationale for further systematic evaluation of anifrolumab in mucocutaneous SLE. Prospective studies and registry data are required to define its efficacy, durability of response, and comparative effectiveness versus other biologic agents such as belimumab.

Conclusion

Oral manifestations of SLE are insufficiently addressed in current therapeutic guidelines and may persist despite standard immunosuppressive or biologic therapy. Our case demonstrates that anifrolumab can induce complete remission of refractory tongue ulcers when other agents, including belimumab, are ineffective. Although published evidence is limited to case reports and small series, emerging data suggest that anifrolumab may offer distinct benefits in oral and other mucocutaneous SLE manifestations. While controlled trials and extension/real-world analyses provide encouraging evidence, further prospective comparative studies are needed to define the relative efficacy and long-term safety of anifrolumab for refractory oral lesions.

Data Sharing Statement

This is a case report without statistical analysis of the raw medical record data. All medical data involving the patient were documented in the patient's medical records. If necessary, more detailed imaging data or laboratory data can be provided by the corresponding author upon reasonable request.

Ethics Statement

Ethical review and approval were not required for the study involving human participants in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this report.

Informed Consent for Publication

The patient agreed to publish her medical data including photographs, and signed the informed consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All the authors declare that they have no conflicts of interest in this medical case report and have not received any financial support.

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