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CASE REPORT

Next Chapter After Belimumab: Anifrolumab to the Rescue

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Abstract

Belimumab is a human immunoglobulin G1-lambda-1 (IgG1-λ) monoclonal antibody that is specific for soluble BLyS human protein, also known as B-cell activating factor (BAFF). Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including belimumab.

On the other hand, anifrolumab blocks the type I interferon receptor (IFNAR1) intercepting interferon-driven immune activation.

Because BAFF and IFNAR1 act in different immune pathways, switching from belimumab to anifrolumab can provide benefit when one axis alone isn't sufficient.

Physicians should exercise caution when considering biological therapy in patients with systemic lupus erythematosus (SLE), which is a chronic, debilitating, and usually progressive autoimmune disease in which the body's immune cells secrete antibodies that attack its own tissues.

This is a compelling and rare case of a woman with SLE who developed Toxic Epidermal Necrolysis (TEN) after treatment with belimumab, and who went to experience a remarkable clinical recovery with anifrolumab – six years later.

Keywords: systemic lupus erythematosus, autoimmune disease, toxic epidermal necrolysis, belimumab, anifrolumab.

Introduction

Systemic lupus erythematosus (SLE) is a rare, chronic autoimmune disease which can vary from mild to potentially life-threatening [1]. The seriousness of SLE can range from mild to severe disease. The disease should be treated by a doctor or a team of doctors who specialize in care of SLE patients. People with lupus that get proper medical care, preventive care, and education can significantly improve function and quality of life. Early diagnosis and effective treatments can help reduce the damaging effects of SLE and improve the chance to have better function and quality of life [2].

SLE treatment consists primarily of immunosuppressive drugs that inhibit activity of the immune system. Traditional treatments (glucocorticoids, antimalarials, immunosuppressants) have limited specificity and are associated with long-term toxicity.

Hydroxychloroquine was approved in 1955 [5] and it became a cornerstone treatment in SLE. Belimumab was the first biologic approved for SLE and the first new lupus drug following hydroxychloroquine.

The era of biologics in lupus is not only reshaping disease control, it's redefining how we understand and treat SLE. By targeting the right pathway at the right time for the right patient, biologics are turning once-refractory cases into quiet disease.

Romanian clinicians can now acces both belimumab and anifrolumab, enabling choice based on disease phenotype, organ involvement, or previous therapy response. Belimumab approved in 2011 by the FDA, was the first biologic specifically approved for lupus in over 50 years, making a major milestone in SLE therapy. About ten years after belimumab's approvel, in 2022, anifrolumab was approved as the next biologic therapy for active, autoantibody-positive moderate-to-severe SLE, especially with mucocutaneous or musculoskeletal manifestations who are receiving standard therapy.

We present the case of a 55-year-old woman with SLE who was treated with belimumab, following two immunosuppressive agents with no clinical and biological benefits. She experienced severe cutaneous adverse reaction after two months of treatment with belimumab. The long interval without biologics, followed by the successful initiation of anifrolumab highlights a clinical turning point.

Case presentation

We present a 55-year-old woman with multiple surgical antecedents in the genital area, diagnosed with SLE 8 years ago, manifesting with cutaneous, musculoskeletal, haematological and immunological

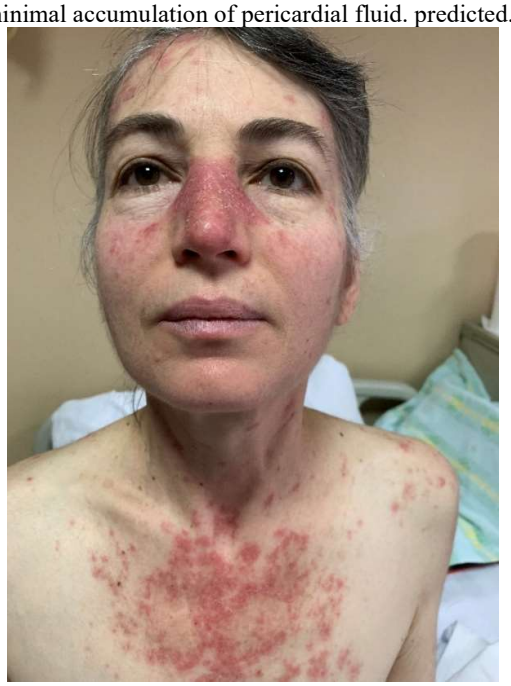
involvement.

At the onset of the disease in may 2017 she presented laboratory findings: anemia, inflammatory syndrome, hypocomplementemia, hyperimmunoglobulinemia and antinuclear antibodies (ANA) and anti-double stranded DNA (anti-dsDNA) positive. The ultrasound of the hands revealed synovitis in a least 3 metacarpophalangeal (MCP) joints with Power Doppler grade II and synovitis of the distal interphalangeal (DIP) proximal joint of the left second finger. The dermatologist pleaded for facial erythemato-squamous skin lesions suggestive for SLE.

Taking into account that the patient met 6/16 points of the revised SLICC criteria (2015) for the SLE diagnosis, she received initially therapy hydroxychloroquine 400 mg daily and low dose of corticosteroids.

After one month of treatment with hydroxychloroquine, she developed cutaneous reaction. A switch therapy regimen was performed to azathioprine (AZA) 100 mg daily, treatment followed from june 2017 to the present. Due to persistent skin disorder she received dapsone (a synthetic sulphone, similar to the sulphonamide drugs, targeting dihydropteroate synthase, a key enzyme in bacteria) as consolidation therapy.

She presented in our department in december 2018 for papulo-squamous skin lesions on face, upper torso and upper back (Figure 1a,b). Laboratory tests showed hemolytic anemia (hemoglobin 9.5 g/dl), lymphopenia, hypocomplementemia. Was also assessed proteinuria to rule out a renal involvement and it was negative (754 mg/24 hours). The patient was screened for ANA and anti-dsDNA antibodies and were positive in a high titer. Electrocardiogram, abdominal ultrasound and chest radiograph were normal. Transthoracic echocardiography revealed minimal accumulation of pericardial fluid. predicted.



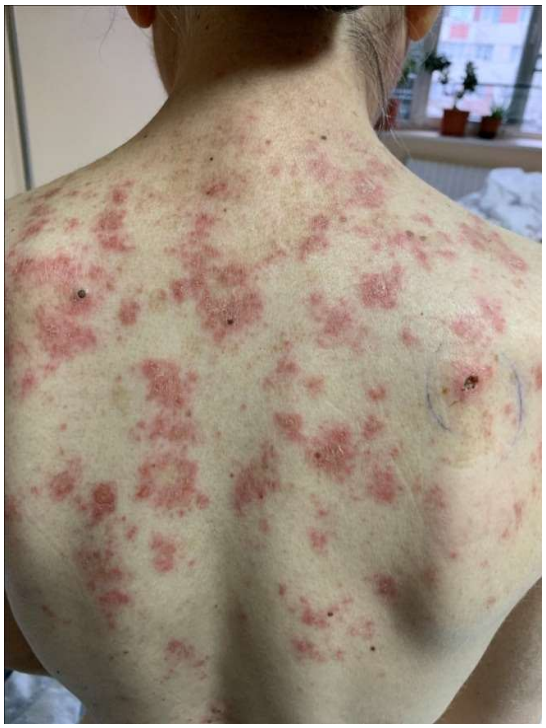


Figure 1a, b. *Papulo-squamous skin lesions*

The dermatologist's opinion was for subacute cutaneous lupus and a skin biopsy from upper back was performed.

The histopathological examination (Figure 2) showed vacuolar alteration of the basal keratinocytes and perivascular lymphoplasmacytic inflammatory infiltrate, findings so characteristic for subacute SLE. So, the patient was treated with pulse IV methylprednisolone therapy 250 mg for four consecutive days associated with gastric protection and potassium and vitamin D supplementation to prevent corticosteroids induced adverse events.

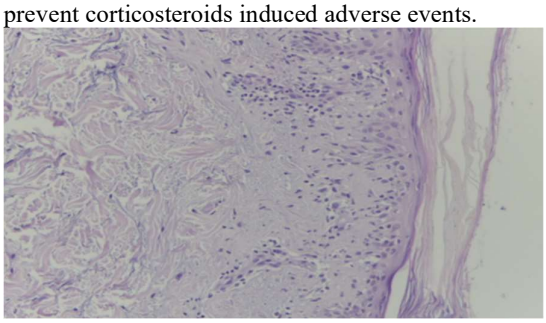


Figure 2. *Histopathological findings showing vacuolar alteration of the basal keratinocytes and perivascular lymphoplasmacytic inflammatory infiltrate*

At that moment, the patient had an intense disease activity based on Erythematosus Disease Activity Index (SLEDAI score) which was 20. For that reason, the patient met the inclusion criteria for the therapy with belimumab, the first targeted therapy for the treatment of SLE approved in Romania in 2018 (she was > 18 years, she have clinical diagnosis of SLE, active SLE disease, autoantibody-positive, on stable

SLE treatment regimen). Thus, she received the first 3 loading doses (day 0, 14, 28) of belimumab in january 2019 and another dose in february after four weeks, when she developed erythemato-bullous lesions with tendency to rapid coalescence which finally leaded to extensive denuded area (Figure 3a, b).

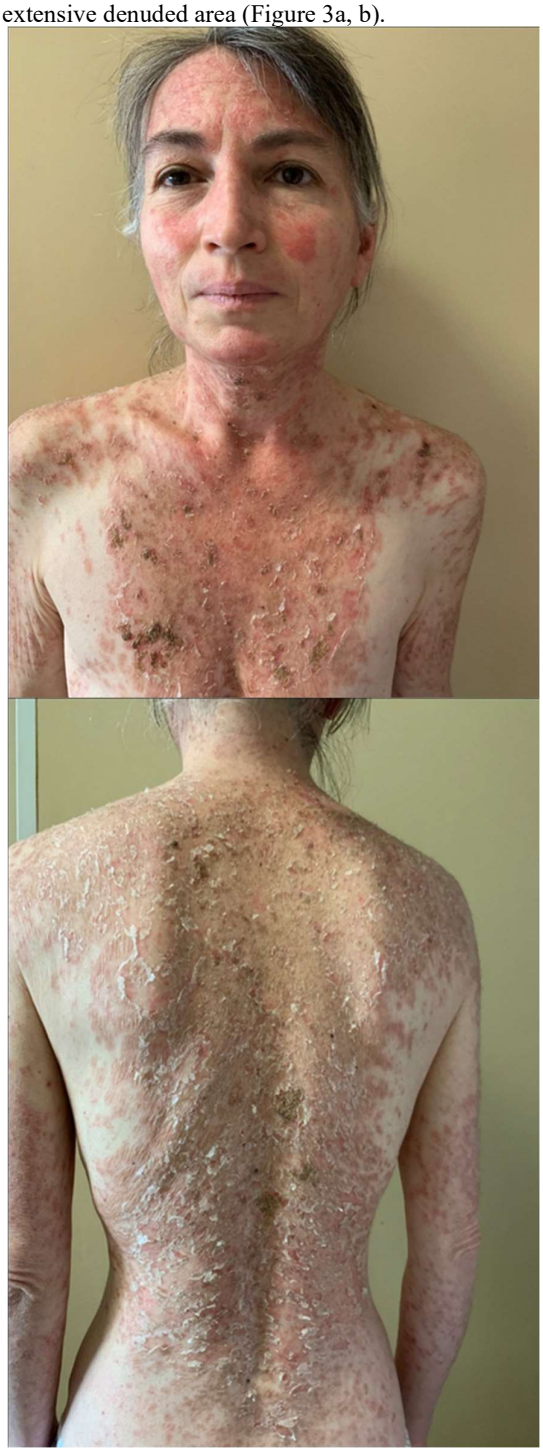


Figure 3 a,b. Erythemato-bullous lesions with tendency to rapid coalescence and epidermal detachment

Laboratory findings showed satisfactory laboratory tests improvement (resolution hemolytic anemia and lymphopenia), being present only hypocomplementemia.This time, the dermatologist stated for the adverse reaction to belimumab. Another skin biopsy was perfomed and it showed epidermal necrolysis with detachment and keratinocyte apoptosis in the basal layer of the epidermis (Figure 4a, b) suggestive for toxic epidermal necrolysis (TEN).

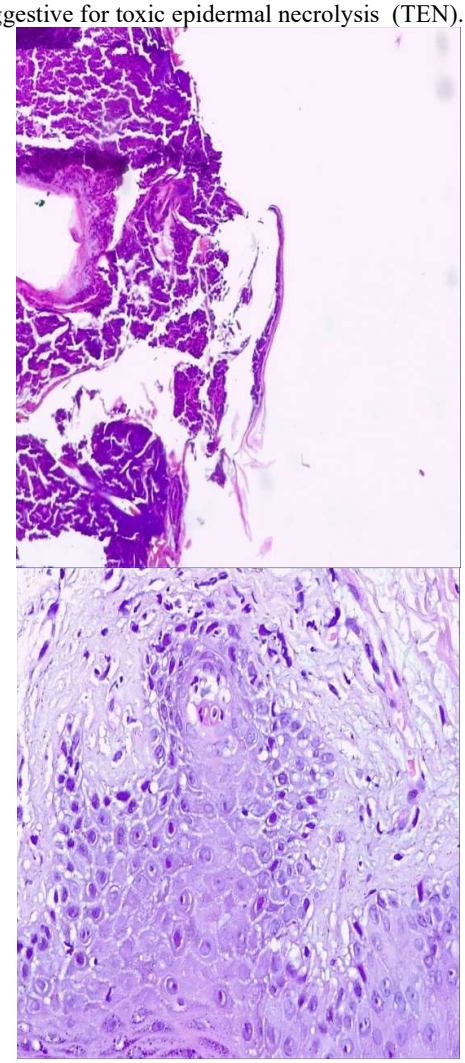


Figure 4 a, b. *Histopathological findings showing epidermal necrolysis with detachment and keratinocyte apoptosis in the basal layer of the epidermis*

TEN is a potentially life-threatening dermatologic disorder characterized by widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes, resulting in exfoliation and possible sepsis and/or death [7]. The average reported mortality rate of TEN is 25-35%; it can be even higher in elderly patients and those with a large surface area of epidermal detachment [8]. A serious cutaneous reaction is more likely to occur during the first 2 months of treatment [9].

The management concentrate on resuscitative and supportive strategies with the primary concern that of avoiding infection. The general measures include immediate withdrawal of all the suspected drugs is the key to the management of TEN [10].

Regarding our patient, belimumab was permanently discontinued and we treated the patient with pulse IV methylprednisolone therapy 500 mg for three consecutive days associated with gastric protection and potassium and vitamin D supplementation to prevent corticosteroids induced adverse events. In the following days, she presented detachment of cutaneous necrosis.

She showed progressive clinical improvement with reepithelialization of the affected skin areas (Figure 5a, b). She was discharged in stable condition after resolution of the acute toxic epidermal necrolysis. Upon recovery, lupus specific treatment was gradually reintroduced (azathioprine 100 mg/day and medium dose of systemic corticosteroid).

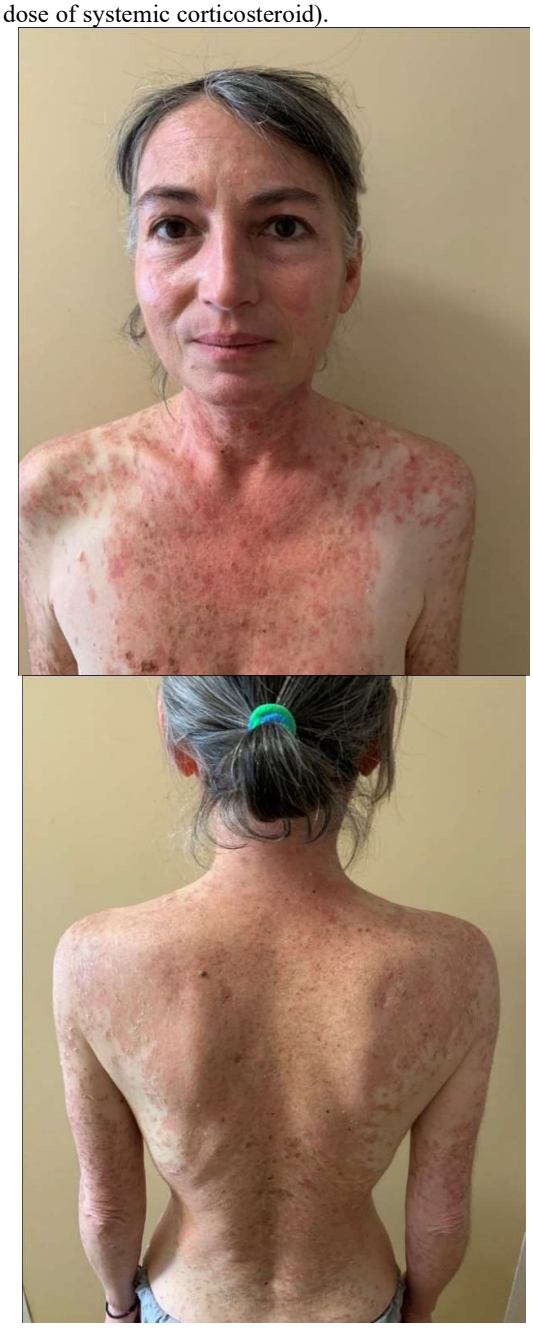


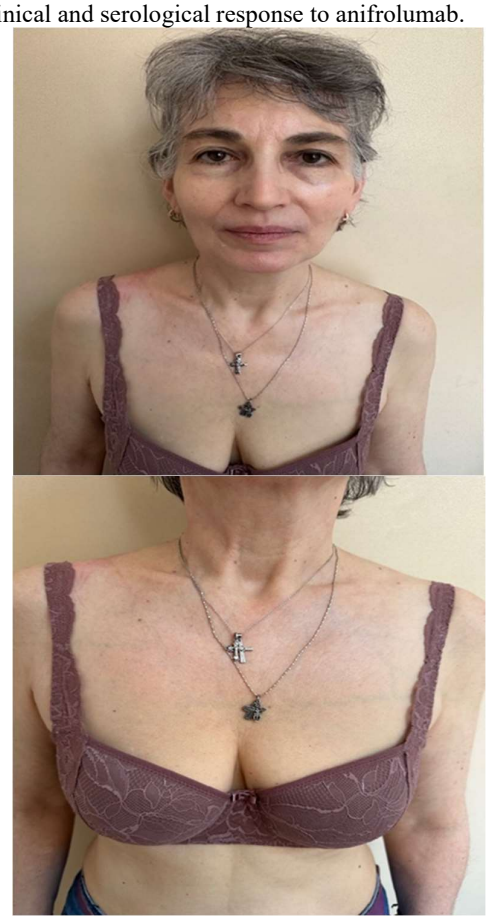
Figure 5 a, b. *Progressive reepithelialization of denuded skin areas*

Between 2019 and 2025 the patient remained on azathioprine and low-dose steroids. Disease activity remained moderately active (SLEDAI score of 10) with recurrent cutaneous flares, arthritis along with persistent hypocomplementemia and occasional leukopenia, in spite of continuous immunosuppression. Her quality of life was impacted by chronic symptoms and insufficient disease control.

In february 2025, after a careful reassessment of her disease profile and taking into account that persistent inflammation cause cumulative and irreversible tissue damage, the patient was evaluated for a new biologic and the decision was made to initiate anifrolumab, based on a distinct mechanism of action and favorable safety profile in cutaneous lupus.

Despite her previous severe reaction to belimumab, the response was excellent. The patient tolerated anifrolumab remarkably well, with no recurrence of TEN or other cutaneous complications.

Also, her skin lesions resolved, joint symptoms diminished significantly (Figure 6 a, b, c, d) and her laboratory profile showed gradual normalization of complement levels (C3 increased from 60 mg/dl to 90 mg/dl, C4 increased from 1.5 mg/dl to 9.8 mg/dl)) and improving leukopenia. Corticosteroid doses were reduced. SLEDAI score decreased significantly within the first 6 months (from 10 to 2). This progressive reduction in SLEDAI score confirms a favorable clinical and serological response to anifrolumab.



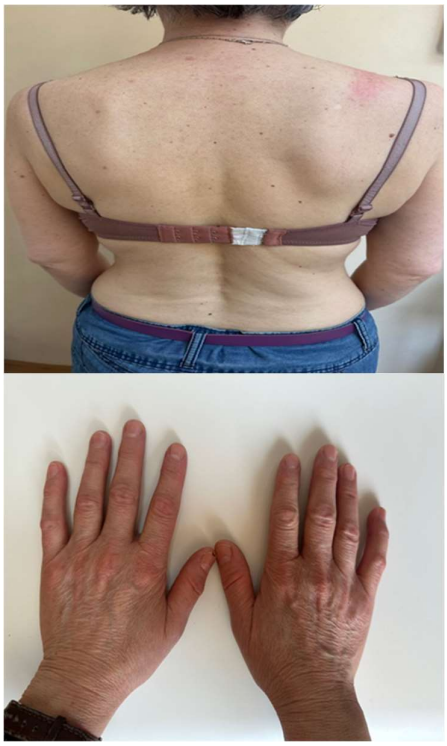


Figure 6 a, b, c, d. *Complete resolution of cutaneous and articular symptoms after 6 months of anifrolumab*

Discussions

Adverse drug reactions are cutaneous manifestations that can occur after the use of any chemical by any route of administration. The best known are erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, considered by some authors as a spectrum of the same disease [11].

TEN in lupus can be triggered by medications, disease flares, or rarely by biologics.

After reviewing the literature, we found no previously reported cases of toxic epidermal necrolysis induced by biologic therapies such as belimumab in patients with SLE. Most available literature on TEN in lupus focuses on TEN-like acute cutaneous lupus eruptions (mimicking TEN), drug-induced TEN like antibiotics, NSAIDs, or rare SLE presentations that resemble TEN at onset.

To our knowledge, this is the first reported case of TEN associated with belimumab in a patient with SLE.

This case underscores the importance of clinical vigilance for rare but severe cutaneous adverse reactions in patients with SLE starting biologic therapy.

Due to their differing mechanism of action, anifrolumab was tolerated in a lupus patient who previously developed TEN in response to belimumab. IFNAR1 blockade affects interferon pathways more broadly and does not rely on BAFF signaling. Anifrolumab does not directly target B cells, which may be involved in delayed hypersensitivity reactions like TEN.

Conclusions

This case demonstrates that life after severe adverse events like TEN is possible in lupus care, and that targeted therapy can still be safe and effective when appropriately selected and monitored – even years after a major complication. The possibility of reintroducing biologic therapy after a severe reaction, provided the new agent has a distinct mechanism of action and careful risk-benefit assessment.

Anifrolumab offered a successful alternative, suggesting the value of switching mechanisms in challenging cases.

A refined comparative overview of belimumab, anifrolumab and rituximab in SLE, supported by recent evidence published in may 2025 demonstrated that Anifrolumab has a strong control over hematologic parameters and complement levels but did not achieve lower dsDNA levels, leaving the clinical significance of this finding unclear. In contrast, Belimumab and Rituximab, despite greater variability in hematologic control, maintained better stability in dsDNA and complement levels [12].

In november 2024, Hsin-Hua Chen, a researcher from Division of Allergy, Immunology and Rheumatology in Taiwan has contributed to the fields of SLE by conducting A Multicenter Cohort Study comparing safety profiles of anifrolumab and belimumab, This study utilized the TriNetX Research Network to analyze real-world data from SLE patients treated with these biologics. This real-world global multicenter matched cohort study provides valuable insights into comparative safety of anifrolumab and belimumab. The authors demonstrated that the risks of adverse events were not significantly different between SLE patients treated with anifrolumab or belimumab. [13].

In lupus, there is no treat-to-target guidelines like in rheumatoid arthritis and are less data and fewer options treatment, but switching biologics in lupus is becoming increasingly relevant, though it's not yet established due to the more limited number of approved biologics for SLE and the complexity of the disease.

Compliance with Ethical Standards.

Conflicts of Interest: The authors declare no conflicts of interest.

Funding: We declare no funding.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from the patient presented in this work.

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