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Anifrolumab in Systemic Lupus Erythematosus (SLE): A Critical Appraisal of Clinical Trials and its Prospects for Elevating Patients' Quality of Life

Nicholas Aderinto[1], Gbolahan Olatunji[2], Emmanuel Kokori[2], Innocent Bonu[2], Varisha Zuhair[3], Doyin Olatunji[4], Ayodeji Akinmeji[5], Shakil Areej[3], Joel Odeyale[6]

1. Department of Medicine and Surgery, Ladoke Akintola University Teaching Hospital, Nigeria
2. Department of Medicine and Surgery, University of Ilorin, Nigeria
3. Jinnah Sindh Medical University, Pakistan
4. Western Illinois University, Illinois, Chicago, USA
5. Department of Medicine and Surgery, Olabisi Onabanjo University Teaching Hospital, Ogun State.
6. Bowen University, Iwo, Osun State

REVIEW

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Corresponding Author:
Olatunji Gbolahan
Department of Medicine and Surgery
University of Ilorin,
Nigeria.
Email: iamapex.og@gmail.com

ABSTRACT

Introduction

Systemic Lupus Erythematosus (SLE) presents a complex autoimmune challenge characterized by chronic inflammation and multi-organ involvement.

Methods

This paper offers a comprehensive analysis of Anifrolumab, a promising monoclonal antibody that targets type I interferon signalling, as a potential treatment for SLE. It also compares with existing therapies, namely Belimumab and Rituximab

Results

Anifrolumab received FDA approval in 2021 based on evidence from clinical trials, such as MUSE and TULIP-2, demonstrating its effectiveness in reducing disease activity, glucocorticoid usage, and flares among SLE patients. However, concerns regarding its safety profile, particularly herpes zoster infections and immunosuppression, should be addressed. Comparative analysis of Belimumab and rituximab reveals their distinct mechanisms of action and levels of clinical evidence. Belimumab, focusing on B-cell activity, has a longer history of reducing disease activity and flares. Rituximab, while promising, lacks direct comparative data. Challenges related to the long-term safety and efficacy of Anifrolumab emphasize the need for personalized treatment strategies, patient selection, and real-world data integration. The paper discusses the importance of tailoring therapies based on biomarker profiles and clinical characteristics, involving patients in shared decision-making, and monitoring treatment responses over time.

Conclusion

The paper highlights ongoing research and clinical trials exploring new therapeutic approaches for SLE, offering hope for improved outcomes. It underscores that Anifrolumab, while promising, should be considered within the context of individual patient needs, with further studies necessary to refine treatment choices for SLE patients.

Key Words

SLE, Anifrolumab, Quality of Life

What this review adds:

This paper collates clinical trials that has been done on Anifrolumab in SLE treatment and examines its efficacy and potential thus drawing inferences from individual studies to make a more concrete recommendation

1. What is known about this subject?

Anifrolumab is an emerging therapy for SLE treatment.

2. What new information is offered in this review?

This review explored findings from different studies and identifies what the consensus is and how it can be used to benefit individuals with SLE.

3. What are the implications for research, policy, or practice?

Improvements in the management of SLE may be obtained by identifying appropriate populations for the use of Anifrolumab.

Introduction

Systemic Lupus Erythematosus (SLE), the most prevalent form of lupus, is an autoimmune disease characterized by the immune system's self-directed attack on bodily tissues, resulting in widespread inflammation and organ damage1. It affects multiple organ systems, including the joints, skin, brain, lungs, kidneys, and blood vessels, leading to a diverse clinical presentation[1]. While the precise etiology of SLE remains elusive, it is understood to be influenced by a complex interplay of genetic, hormonal, and environmental factors[1].

Notably, SLE disproportionately affects women of childbearing age[2]. The hallmark of SLE lies in the presence of autoantibodies targeting nuclear and cytoplasmic antigens, underpinning its pathogenesis[3]. Clinical manifestations vary from mild cutaneous symptoms to severe organ involvement, such as renal failure, pulmonary hypertension, and cardiac dysfunction[4]. Treatment strategies are tailored based on disease severity and the specific organs affected. However, SLE's unpredictable course, characterized by alternating flare-ups and remissions, presents significant challenges with potential implications for life expectancy, particularly in cases involving critical organ damage.

Anifrolumab, an IgG1κ monoclonal antibody that inhibits the type 1 interferon receptor, has emerged as a potential therapeutic option for adults with moderate to severe SLE5. By targeting IFN-alpha activity, Anifrolumab aims to mitigate the inflammation associated with organ damage in SLE patients. This paper examines Anifrolumab's therapeutic potential in the context of SLE. Our exploration will encompass the molecular mechanisms underlying Anifrolumab, its performance in clinical trials, and it's associated adverse effects. Clinically, it is marked by periods of remission and flare-ups, presenting a complex interplay of metabolic disturbances and deficiencies in minerals and vitamins. These are further compounded by systemic symptoms involving arthritis, nephritis, vascular events, and damage to organs like the heart, Central Nervous System (CNS), kidneys, and skin. These factors contribute to elevated morbidity and mortality among SLE patients[6]. It's worth noting that individuals of Black, Asian, and Hispanic ethnicities have a higher prevalence and incidence of this condition [7].

Recent data reveals varying SLE incidence rates across different regions, such as North America (ranging from 3.7 to 49.0 per 100,000 person-years in the US Medicare population), Europe (1.5 to 7.4 per 100,000 person-years), South America (1.4 to 6.3 per 100,000 person-years), and Asia (2.5 to 8.6 per 100,000 person-years). Unfortunately, reliable estimates for SLE prevalence in Australasia and Africa are unavailable. The prevalence of SLE also varies widely, with figures ranging from 48 to 366.6 per 100,000 people in North America, 29.3 to 210 in Europe, 24.3 to 126.3 in South America, 20.6 to 103 in Asia, 13 to 52 in Australasia[8], and 601.3 to 7,713.5 in Africa. Additional epidemiological research in North America has reaffirmed that SLE disproportionately affects women and individuals from racial and ethnic minorities. SLE is approximately nine times more prevalent in women (constituting 85-93 Per cent of SLE cases) than men. This gender disparity begins to emerge significantly in women during adolescence, while in men; it progresses more gradually and evenly throughout life[9]. Notably, severe organ involvement, particularly renal disease, continues to be prevalent in Asia.

Existing Therapies for SLE

SLE treatment strategies primarily revolve around achieving remission, preventing flare-ups, ensuring long-term survival, avoiding organ damage, and enhancing the quality of life. This is achieved by managing disease activity and reducing comorbidities and medication-related side effects[10]. Nutritional therapy, including dietary restrictions on carbohydrates and proteins and nutritional supplements such as vitamins, minerals, and polyphenols, has emerged as a potential approach to mitigate inflammatory responses in SLE. Nutritional supplements, including calcium and vitamins, may offer preventive benefits with fewer or no adverse effects compared to traditional pharmaceutical therapies.

Recommended pharmacological treatments encompass anti-malarial drugs, glucocorticoids (GC), non-steroidal anti-inflammatory drugs, and targeted therapies. Targeted treatments directly or indirectly modulate B-cell survival and activation, resulting in B-cell depletion or suppression and consequently reducing autoantibody production. Glucocorticoids have long served as foundational medications in SLE treatment due to their rapid effectiveness in controlling disease flares.

However, they are associated with significant side effects. Recent research indicates that higher GC dosages are often unnecessary and may lead to organ damage. Current SLE therapy adopts a "treat-to-target" approach, focusing on achieving specific levels of remission or low disease activity. This approach incorporates immunosuppressive therapy and biologics to attain minimal disease activity or, ideally, remission without using GCs. Precise assessment of disease activity is crucial in developing a long-term treatment plan to reduce or discontinue GC medication. However, the

ultimate treatment decision is collaborative between the patient and the physician, considering factors such as disease activity, risk of flare-ups, and cumulative damage. Non-corticosteroid immunosuppressant's target various B cell populations, including cyclophosphamide, azathioprine, and mycophenolate mofetil. The biologics belimumab and anifrolumab, monoclonal antibodies, are approved for SLE treatment. Resistance to standard therapy involving GCs and non-corticosteroid immunosuppressants is common in SLE patients, leading to ongoing clinical trials evaluating biologics for individuals with insufficiently managed disease using conventional medications.

It is important to note that responses to existing medications vary among SLE patients, highlighting the need for novel therapeutic options. Immunological profiling and precision medicine guided by transcriptomics analysis can aid in identifying distinct immunological phenotypes and gene signatures in SLE patients[11]. This can enhance our understanding of the disease's pathophysiology and enable tailored therapies, ultimately improving clinical outcomes. In the long term, this innovative approach can potentially identify new therapeutic targets and prognostic biomarkers for SLE. The rising prevalence of resistance to standard SLE treatment is a cause for concern, necessitating prompt action to initiate new clinical trials to enable patients to lead lives free from relapses, if not entirely free from SLE.

Anifrolumab Mechanism of Action

Anifrolumab functions as a type 1 interferon alpha-beta receptor (IFNAR) inhibitor and is authorized for treating SLE. It exhibits a prolonged duration of action, requiring administration only once every four weeks. The mechanism of its action involves the interference with the type 1 interferon receptor (INFAR1) pathway, which is activated by various interferons, including alpha, beta, epsilon, kappa, and omega, leading to the stimulation of gene transcription[12]. Activation of INFAR1 and INFAR2 results in the phosphorylation of STAT1 and STAT2, followed by their translocation and interferon regulatory factor 9 (IRF9) into the cell nucleus. This cascade activates the interferon-stimulated response element (ISRE), subsequently triggering the activation of numerous inflammatory and immune-modulatory proteins. Additionally, INFAR1 activation stimulates the maturation of certain immune cells, such as monocytes, into dendritic cells[12]. It exerts its therapeutic effect by selectively binding to subunit 1 of INFAR1, thereby inhibiting the receptor's activity and down regulating signaling and gene transcription of inflammatory and immune-modulatory proteins. The Fc region of anifrolumab features a triple mutation (L234F/L235E/P331S) designed to prevent its binding to cell surface Fc receptors. Consequently, anifrolumab acts as a blockade, preventing IFN-1 from transmitting signals to other immune cells, effectively thwarting the body's autoimmune attacks on itself.

Pre-clinical studies on Anifrolumab

Anifrolumab received approval for medical use in the United States in July 2021 and the European Union in February 2022, notably as a first-line therapy in the United States. To gain insights into the pathogenesis of SLE, researchers traditionally employed mouse and monkey models to investigate the underlying mechanisms of the disease. One key focus was activating the type I interferon (IFN) pathway, which has been implicated in SLE pathogenesis at the genetic and gene expression levels. All type I IFN cytokines signals through the interferon-α/β receptor (IFNAR). Early-phase studies revealed that anifrolumab, a human monoclonal antibody targeting IFNAR subunit 1, displayed an acceptable safety profile. It also demonstrated the ability to attenuate transforming growth factor beta (TGF-β)-mediated fibrosis in SLE skin, supporting its continued clinical development [13, 14].

Janus kinase (JAK) signaling pathways, downstream from IFNAR, emerged as potential targets to block deleterious IFN and other pro-fibrotic cytokine activation in SLE. Interferon regulator factors (IRF) 5, 7, and 8 were identified as contributors to the pro-fibrotic response in SLE preclinical studies, making them promising therapeutic targets. Depletion of plasmacytoid dendritic cells (pDCs), which attenuate IFN activation and the fibrotic response in vitro and murine models, is also being considered as a viable drug target for future clinical studies[15].

To assess the safety of anifrolumab during pregnancy and postnatal development, pregnant cynomolgus monkeys received intravenous anifrolumab every two weeks from Gestation Day 20 through the gestation period and up to one month post-partum. The study found no evidence of anifrolumab-related maternal toxicity, embryo-fetal toxicity, or post-natal developmental effects. Importantly, there were no observed effects on T-cell-dependent antibody response in the infant monkeys up to Day 180 after birth. The No Observed Adverse Effect Level (NOAEL) for maternal and developmental toxicity was determined to be 60 mg/kg[16].

In infant cynomolgus monkeys, serum concentrations of anifrolumab on Day 30 after birth increased with dose and ranged from approximately 4.2 Per cent to 9.7 Per cent of maternal concentrations. Anifrolumab concentrations in the infant serum were notably higher than in maternal milk, suggesting placental transfer. However, due to species-specific differences in lactation physiology, these animal

data may not accurately predict human drug levels[17]. The carcinogenic and genotoxic potential of anifrolumab in humans has not been evaluated, but rodent models of IFNAR1 blockade have shown an increased carcinogenic potential. The clinical relevance of these findings remains unknown. Additionally, animal models have not directly studied the impact of anifrolumab on male and female fertility.

Clinical Trials and Significance

Anifrolumab has brought significant improvements in the quality of life for SLE patients. Conducting individual risk-benefit assessments and engaging in shared decision-making when determining the appropriate therapy for each patient is crucial. Several key studies have compared the benefits and risks of anifrolumab with previous standard therapies like steroids, antimalarial, and immunosuppressant's (Table 1). Some noteworthy trials include the Treatment of Uncontrolled Lupus via the Interferon Pathway (TULIP), SLE Disease Activity Index (SLEDAI), British Isles Lupus Assessment Group Index (BILAG), modified Cutaneous Lupus Erythematosus Disease Area and Severity Index (mCLASI), and others[18].

Anifrolumab has relatively higher costs compared to conventional SLE treatments. It showed fewer incidents of serious depression and treatment-emergent suicidality compared to Belimumab. Patients treated with anifrolumab reported significant improvements in health-related quality of life, including reductions in pain, fatigue, mood disturbances, and improvements in physical function. Anifrolumab consistently improved both skin rash and arthritis across multiple disease measures, compared to placebo, in patients with moderate to severe SLE. Patients with moderate to severe SLE had a higher likelihood of achieving improved disease activity with anifrolumab compared to belimumab[19].

Anifrolumab has demonstrated its benefits across a broad population of adult patients with moderate to severe SLE who are receiving standard therapy. It provides a valuable option to manage disease activity while minimizing the burden of corticosteroid use. Long-term safety assessments and clinical trials, including the phase 2b MUSE trial and phase 3 TULIP-1 and TULIP-2 trials, have played pivotal roles in assessing the effectiveness of anifrolumab. In the MUSE trial, anifrolumab showed significant efficacy, with notable improvements in the SLE Responder Index (SRI-4) at week 24, particularly in patients with higher type I interferon signatures[18]. The TULIP-1 trial focused on patients with moderate to high-severity SLE and found potential benefits of anifrolumab in reducing oral corticosteroid doses. In the TULIP-2 trial, anifrolumab demonstrated its potential by achieving a significant BICLA response at week 52, indicating improved management of lupus disease activity, especially in patients with a high interferon gene signature. Pooling data from TULIP-1 and TULIP-2 trials revealed reduced annualized flare rates, delayed onset of the first flare, and fewer patients experiencing flares, particularly in organ systems typically affected at the study's outset[18-20]. An extension study of patients who completed the MUSE trial demonstrated sustained disease activity improvement over three years, further supporting anifrolumab's long-term safety and efficacy. Another extension study included patients from the TULIP trial and revealed fewer serious adverse events among those receiving anifrolumab, suggesting its favourable long-term safety and tolerability.

A multicentre open-label study in Japanese SLE patients further confirmed anifrolumab's well-tolerated profile, highlighting its potential to suppress the type I interferon gene signature[21]. Belimumab, a human immunoglobulin G1λ (IgG1) monoclonal antibody, inhibits the biological activity of B-lymphocyte stimulating protein and has been approved for the treatment of patients aged 5 years or older with SLE in over 75 countries[22]. Patients treated with belimumab plus ST has consistently demonstrated a reduction in disease activity, glucocorticoid use, and frequency of flares compared to placebo plus ST in randomized controlled trials [23].

Rituximab (RTX), a chimeric mAb specific for CD20, has made a successful foray into rheumatology, being beneficial in managing rheumatoid arthritis and ANCA-associated vasculitides. It was first explored for SLE in 2002 when five out of six patients with refractory disease clinically responded to a combination of RTX, CYC, and high-dose corticosteroids [24,25].

There have been no randomized control trials comparing the efficacy of available biological agents against each other in the management of SLE. However, several indirect comparisons have been made, with anifrolumab- and belimumab-treated patients more likely than placebo-treated patients to achieve a sustained reduction in oral corticosteroids (OCS) dose during the first year of therapy. After adjusting for cross-trial differences, anifrolumab (300 mg iv.) was associated with significantly greater treatment benefits than belimumab (10 mg/kg iv.) in outcomes of SLEDAI response and SRI-4 response at 52 weeks[26].

Implemented a PAIC of RCT data to evaluate the efficacy of belimumab versus anifrolumab at 52 weeks in adults with SLE. The results suggest that belimumab and anifrolumab are generally comparable in terms of SRI-4 at 52 weeks, but could not rule out the possibility of a clinically meaningful benefit for either treatment[19]. It was Anifrolumab did not

increase depression, suicidality, or the need for antidepressants when compared with standard therapy. In comparison to the placebo, the treatment of uncontrolled lupus via interferon pathway, the TULIP-2 trial showed that anifrolumab achieved composite endpoints of disease-activity response, a decline in the glucocorticoid dose, and reduction in the severity of skin disease over 52 weeks. These therapeutic benefits appear to be sustained over longer-term treatment[18].

However, there are several challenges and considerations related to Anifrolumab's safety profile, including adverse effects such as upper respiratory tract infections, nasopharyngitis, infusion-related reactions, bronchitis, and urinary tract infections. HZ infections were higher among anifrolumab-treated patients than placebo, and severe adverse events like pneumonia were reported. Compared with placebo, anifrolumab was associated with lower annualized flare rates, prolonged time to first flare, and fewer patients with ≥1 flare, as well as flares in organ domains commonly active at baseline. In a pooled analysis of TULIP-1/TULIP-2 in patients with moderate to severe SLE, anifrolumab treatment reduced annualized flare rates and extended time spent flare-free compared with placebo.

Jayne, et al. Reported that the number of patients who developed new BILAG 1A or 2B flares at any time during the study was reduced by 28 Per cent and 29 Per cent, and the numbers who developed new BILAG A flares were reduced by 46 Per cent and 35 Per cent, in the anifrolumab 300-mg and anifrolumab 1,000-mg groups, respectively[27].

There have been reported Serious Adverse Events (SAEs) in nivolumab-treated patients including pneumonia; some were deemed unrelated to treatment. One patient in the placebo group in a Randomized Controlled Trial (RCT) died of community-acquired pneumonia, which was assessed as related to treatment.

Quality of life improvement is another important aspect of Anifrolumab's use. The attainment of a Lupus Low Disease Activity State (LLDAS) is associated with improved patient outcomes and quality of life. Body image, fatigue, family relations, and disease impact on professional and social life are important elements of quality of life for SLE patients[28].

To achieve optimal treatment, it is imperative to develop tailored Treatment Strategies as SLE is renowned for its remarkable heterogeneity, characterized by diverse clinical manifestations and disease courses among patients. To tackle this diversity effectively, we should develop tailored treatment plans based on biomarker profiles and clinical characteristics. By categorizing patients into subgroups sharing similar disease traits, we can customize treatment approaches to address the unique requirements of each subgroup. It is equally vital to embrace shared decision-making; Engaging patients in shared decision-making processes is fundamental to personalized medicine. Patients should actively participate in treatment decisions, considering their values, preferences, and treatment goals. This collaborative approach fosters a sense of ownership and empowerment, ultimately contributing to better treatment adherence and patient satisfaction.

Furthermore, there is a need for Real-World Data Integration; As anifrolumab enters the clinical landscape, real-world data should be integrated into patient selection and personalized treatment approaches. Observational studies and registries can provide valuable insights into treatment responses, long-term outcomes, and safety profiles, further refining personalized medicine strategies[21].

Future Prospects

Systemic Lupus Erythematosus (SLE) treatment has seen significant progress. Belimumab, a monoclonal antibody targeting B-cell activating factor, was approved for SLE patients and lupus nephritis30. New therapies targeting different molecular pathways have emerged, including Anifrolumab, BIIB059, omalizumab, and IFN-α kinoid[31, 32]. Kinase inhibitors like baricitinib and tofacitinib have effectively reduced skin and joint manifestations in SLE.

Immunomodulators like iguratimod and therapies involving mesenchymal stem cells are being explored[33]. However, SLE remains a heterogeneous disease, and tailoring treatments to specific pathways is crucial. Ongoing clinical trials continue to investigate new therapeutic approaches, with results expected to bring more options for SLE patients[34].

Conclusion

The anti-type-1 interferon drug anifrolumab shows potential as a treatment for systemic lupus erythematosus (SLE). It has inherent limitations such as frequent adverse effects such as upper respiratory tract infections and infusion-related responses. Nonetheless, it remains a promising therapeutic agent in ensuring patients with SLE have improved outcomes.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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Figures and Tables

Table 1: **Overview of Clinical Trials**

Clinical Trial	*Authors*	*Year*	*Sample Size*	*Findings*
MUSE Phase IIb	Richard Furie et al.	2017	305	Anifrolumab substantially reduced disease activity and improved SRI-4 at 24 and 52 weeks.
TULIP-1 Phase III	Richard Furie et al.	2019	457	Anifrolumab didn't surpass placebo in the primary SRI-4 at week 52, but secondary endpoints, including corticosteroid reduction and BICLA responses, suggest potential clinical benefits.
TULIP-2 Phase III	Eric F Morand et al.	2019	362	Anifrolumab group achieved a higher BICLA response than placebo group at week 52.placebo
MUSE Long Term Extension	W Winn Chatham et al.	2021	246	Long-term anifrolumab treatment demonstrates an acceptable safety profile with sustained improvement in SLE disease activity and serologic measures.
TULIP Long Term Extension	Kenneth C Kalunian et al.	2022	547	favorable benefit-risk profile of anifrolumab for patients with moderate-to-severe SLE
Phase II, open-label study in Japanese population	Yoshiya Tanaka et al.	2019	20	Adverse effects with same for all doses of Anifrolumab and it was well tolerated by patients.

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