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PROGRESSION AND PERSPECTIVE, A 20-YEAR RETROSPECTIVE ON SYSTEMATIC LUPUS ERYTHEMATOSUS THERAPEUTICS: A NARRATIVE REVIEW

Internal Medicine

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ABSTRACT

This study aims to examine efficacy and safety of current regimen in comparison to novel therapeutic regimens with treat-to-target strategies and agents consisting of non-steroidal immunosuppressants, biologics, and nonpharmacologic treatment options. This study also highlights future treatment options under investigation, aiming to identify potential avenues for improved patient care and disease control. Novel therapies have shown greater improvements in treatment of SLE which would cause decrease in use of steroids and more patient specific targeted therapies. This will help in identifying any knowledge gaps and propose future research directions to address the same and contribute to the enhancement of patient outcomes and quality of life by providing insights into optimal approaches to SLE management.

KEYWORDS

INTRODUCTION:

This study aims to comprehensively evaluate the current understanding of Systemic Lupus Erythematosus (SLE) including its etiology, and pathogenesis, and most importantly; explore the safety profile and the effectiveness of both conventional treatments from 2 decades ago as well as current and emerging therapeutic regimens to provide a nuanced overview of the disease's complexities. According to a recent systematic analysis done globally, the incidence of SLE in men and women is 5.14 and 8.82 per 100,000 person-years, respectively, with a prevalence of 43.7 and 78.73 per 100,000 persons, respectively, with the most newly diagnosed cases in the USA, Poland, and Barbados [1]. Two decades ago, systemic lupus erythematosus (SLE) treatment relied on conventional immunosuppressive agents like corticosteroids, antimalarials, and cytotoxic drugs [2].

Introduction to SLE:

Within the field of autoimmune disorders, Systemic Lupus Erythematosus (SLE) presents a significant challenge due to its diverse clinical presentation and unpredictable progression. SLE is a chronic autoimmune disease with multi-organ and multi-system involvement. A wide range of genetic, immunologic, hormonal, and environmental factors are involved in its pathogenesis.[3] This multifactorial pathogenesis along with its wide variety of phenotypic presentation and constantly fluctuating clinical features and disease progression in an individual makes it difficult to design an accurate disease-targeted and disease-specific treatment.[3][4]. Newer targeted immunomodulation and immunosuppression therapies weigh more in the benefits of the patient than the conventional therapies including anti-malarial and decease modifying anti-rheumatic drugs.[4]

Etiology And Pathogenesis:

SLE pathogenesis includes an interaction between environmental factors and genomic predilection, and the interaction between them alters the genetic expression of the genes that contribute to SLE development. For genetically predisposed individuals, exposure to environmental variables like UVB radiation, toxins, viruses, etc can cause a loss of immune tolerance and aberrant activation of the immune system [5].

Genetic Predisposition to SLE

SLE is associated with many genetic alleles that are associated with the pathogenesis of SLE, most of which are associated with immune modulation and cytokine production [6].

Environmental Triggers

The reason individuals with similar environmental exposure have differences in their disease status is due to differences in their genetic makeup, which also explains the increased chances of suffering from SLE in monozygotic twins. Environmental triggers have been found to damage human cells, resulting in a rise in apoptotic cell load and the escape of self-antigens from apoptotic cells like DNA, nucleic proteins, nuclear RNA, and cell surface molecules [6].

Environmental Triggers which is conventionally found to have a connection with the SLE disease process, and flare-ups are UV light exposures, infections, hormones, medications like smoking, and environmental toxins [7]. Certain medications, like procainamide, antihypertensives for pregnancy like hydralazine, and antiepileptics such as phenytoin, are also found to be connected with dysregulation of the immune system and autoantibody production, leading to drug-induced lupus.

Dysregulation of Innate Immunity.

Over half of patients suffering from SLE have dysfunction of the innate immune system such as upregulated TNF-alpha levels found in their neutrophiles and immune cells [8]. Toll-like receptors are a type of PRR (pattern recognition receptors) that have a crucial part in the functioning of the innate immune system and are associated with autoantibody production in mouse models [9].

Aberrant Adaptive Immune Responses

Adaptive immune dysfunction in SLE includes Hyperactivity of B-cells, cytokines imbalance, and T-cell dysfunction.

The T helper, NK natural killer, IFN interferon, TNF tumor necrosis factor, IgG immunoglobulin G, APC antigen-presenting cell, and SLE systemic lupus erythematosus [8].

Emerging Concepts in SLE Pathogenesis

Epigenetics has been well established in the pathogenesis of SLE recently with modifications like DNA methylation, DNA hydroxymethylation, and Histone modification.

Older Treatments And Current Treatments

The optimal choice of drug therapy for an SLE patient is based on a treat-to-target principle which is a combination of subjective criteria including symptoms, organ involvement, previous therapy and effectiveness, severity, etc. along with the objective criteria like SLE disease activity index(SLEDAI) which eventually help to form a patient-centred approach. [10]

Treatments Two Decades Ago:

Antimalarials:

Hydroxychloroquine was frequently used to reduce symptoms such as joint pain, skin rashes, and fatigue. It also helps prevent lupus flare-ups.

In the context of these analyses, the LUMINA cohort comprised 608 individuals, including Hispanics from Texas and Puerto Rico, African Americans as well as Caucasians. Over a median follow-up period of 39 months, 61 deaths were recorded. Among these, 17 deaths occurred in individuals using hydroxychloroquine at T0, representing 5% of the 349 patients, while 44 deaths were observed in those not using it, accounting for 17% of the 259 patients ($p<0.0001$). To delve deeper into these results, 183 patients with similar disease durations were chosen at random to serve as controls for the 61 patients who passed away, maintaining a 3:1 ratio.

These findings strongly advocate the use of hydroxychloroquine as a potential treatment for all patients diagnosed with Systemic Lupus Erythematosus (SLE). Nevertheless, it is crucial to strictly adhere to established guidelines when administering hydroxychloroquine to ensure accurate dosage, with a maximum limit of 6.5 mg/kg of ideal body weight. Additionally, regular ophthalmological monitoring is imperative to guarantee patient safety and reduce the likelihood of potential side effects.[11]

Corticosteroids:

Prednisone and other corticosteroids were (and still are) used to quickly reduce inflammation and control severe symptoms. Its rapid action profile is particularly useful for acute flares. The non-genomic mechanism of operation of Glucocorticoids where inflammatory and immune modulation occurs by various pathways is particularly useful as it is quick and more potent than the genomic mechanism of operation and more sensitive to higher doses of steroids used during acute flare [12]

During the earlier part of the 20th century, Systemic Lupus Erythematosus (SLE) was commonly regarded as a rapidly progressing and almost always fatal disease. However, since the 1950s, there has been a notable improvement in the rates of survival of SLE patients in developed countries, rising from less than 50% to over 95%, with similar improvements seen in 10-year survival rates.

While the exact safe threshold for glucocorticoid (GC) treatment is not defined, doses below <7.5 mg of prednisone per day are believed to minimize adverse effects. When combined with hydroxychloroquine (HCQ) and judicious use of immunosuppressive drugs, this approach helps to keep prednisone therapy within these safer limits. [13]

Immunosuppressants:

Medications like azathioprine, methotrexate, and mycophenolate mofetil were in use during the early 2000s to suppress the overactive immune system in SLE patients with intense severity.

The use of Conventional Immunosuppressants has become an essential part of management in patients with SLE. In addition to their role in modulating the immune system, these medications also facilitate a faster and more effective reduction in glucocorticoid (GC) doses.

Studies from preliminary RCTs have demonstrated that combining GCs with cyclophosphamide (CYC), rather than using GCs alone, leads to better outcomes for patients suffering from Lupus Nephritis (LN). This combination therapy has been connected to improved renal outcomes and higher rates of remission. However, it is crucial to remember that this approach also comes with an elevated danger of infections and ovarian failure. As a result, it is crucial for healthcare providers to carefully consider the potential benefits and risks when selecting treatment options for SLE patients, especially those with LN.[14]

A follow-up study conducted in December 2004 on participants from the European Trial of Lupus Nephritis (ELNT) has confirmed that in cases of lupus nephritis, employing a treatment strategy aimed at inducing remission with low-dose intravenous cyclophosphamide (IV CYC) accompanied later by azathioprine (AZA) produces clinical outcomes that are on par with those achieved using a high-dose regimen. Moreover, the study's results suggest that an early positive response to this therapeutic approach may serve as an indicator of promising long-term renal outcomes. These findings underscore the potential effectiveness of this regimen and the importance of monitoring patient responses to treatment in the treatment of lupus nephritis.[15] Methotrexate has shown a steroid-sparing effect[16].

Current Treatments Modalities:

Hydroxychloroquine:

HCQ being one of the oldest and most studied drugs for SLE, with proven symptomatic and mortality benefits from the past couple of decades as well as the present should be prescribed to all patients within the given recommendations[17] of 5 mg/kg/day with a daily maximum of 400mg, unless contraindicated. Antimalarials are generally well tolerated apart from serious and rare side effects like ocular toxicity, but the risk can be reduced by dosage monitoring and regular ocular examinations.

Steroids:

Glucocorticoids continue to be the mainstay of SLE treatment due to their potent anti-inflammatory and immunosuppressive effects. According to the European Alliance of Associations for Rheumatology recommendations[17], Glucocorticoids should be used as bridging therapy during acute flares and the maintenance period should be kept as small as possible with a dose of not more than 5mg/day of prednisone equivalent as long term treatment, even with low doses has been linked to an increased case of cataracts, heart disease, osteoporosis, infections, etc.

Immunosuppressants:

Azathioprine, mycophenolate mofetil, and cyclophosphamide are commonly used immunosuppressants in patients with SLE, targeting aberrant immune responses and preventing organ damage. According to the European Alliance of Associations for Rheumatology recommendations, in 2023 [17] patients not responding to HCQ as well as GCs should be started on Immunosuppressants; CYC and rituximab should also be used in patients with organ/life-threatening disease. Patients with acute flare-ups and acute end-organ damage, such as acute lupus proliferative nephritis, thrombocytopenia, etc., should be treated with a combination of GC and CYC.

Voclosporin, approved by the FDA in Jan 2021; belongs to a family of calcineurin inhibitors along with cyclosporin and tacrolimus and has been approved for the treatment of lupus nephritis along with steroids and MMF as it was shown to have a higher response rate than placebo with steroids and MMF in some trials. [18] [19]

Biologic Agents:

By focusing on particular immunological pathways linked to the etiology of the disease, biological treatments have transformed the management of SLE today and represent the largest difference between the treatment choices of the past and now. The first licensed biologic for SLE is a monoclonal antibody called Belimumab against B-lymphocyte stimulator (BLy-S). In a RCT [20] it has demonstrated efficacy in reducing disease activity, and severe flares and was better tolerated in patients receiving placebo. It has also shown faster and higher response in Lupus nephritis patients [21]

Atacicept which is a transmembrane activator calcium moderator and interacts with cyclophilin ligand(TACI) is an antagonist to both Bly-S and proliferation-inducing ligand (APRIL) which are members of the TNF cytokine group. A phase IIB trial called ADDRESS trial [22] showed the efficacy of Atacicept concerning patients with significant disease activity and active serology with a tolerable safety profile.

Another biologic used in patients suffering from SLE is Anifrolumab which works to inhibit the signalling of Type I interferons which is implicated in the mechanism behind SLE. Anifrolumab was FDA-approved in July 2021 for IV/SC use in SLE patients with moderate and severe illness. In a phase 3 trial, Anifrolumab showed a greater proportion of patients having a response at 52 weeks than placebo; with a notable difference in the patient group with higher interferon

gene signature [23]. It has also improved in reducing flare rates and oral corticosteroid reduction.

Rituximab is an anti-CD20 monoclonal antibody, targeting B-cell depletion. 91% of patients with SLE who took rituximab off-label demonstrated some improvement in one or more clinical symptoms, according to a comprehensive analysis of such cases [24].

A retrospective cross-sectional study in Sudan of Rituximab in Lupus nephritis patients showed remarkable clinical and laboratory improvement at the 6-month mark [25].

Interleukin inhibitor like Tocilizumab, an IL 6 inhibitor is also shown to have positive outcomes in patients with SLE. An improvement in refractory fever as well as arthralgia in SLE patients in China was observed while treating them with Tocilizumab who were not responding to corticosteroids and antibiotics [26].

Table 01. Similarities and differences among both old and new treatment modalities

SIMILARITIES	DIFFERENCES
1) Hydroxychloroquine	1) Biologics
2) Immunosuppressants	2) More steroid-sparing strategies
3) Steroids	3) More Personalized Treatment now
	4) More targeted therapies with less reliance on high-dose corticosteroids and more focus on minimizing long-term side effects

Non-Pharmacologic Interventions:

Non-pharmacologic interventions like diet, comorbidity management, etc can be helpful in patients with SLE. For example, Vitamin D insufficiency is more common in SLE patients due to various reasons like sun avoidance due to photosensitivity, renal insufficiency, corticosteroid use, etc. Vit D deficiency has shown a higher degree of fatigue, higher disease activity, cardiovascular risk, etc when it comes to SLE patients. Cholecalciferol supplementation has shown improvement in suppressing disease activity and improving fatigue in SLE patients of juvenile-onset [27].

Although no specific dietary recommendations for SLE patients are present, patients with SLE who follow the Mediterranean diet have lower cardiovascular risk and disease severity [28]. Omega 3 fatty acids intake and the lower ratio of omega 6: omega 3 in the diet have shown positive patient-reported outcomes in SLE activity and better sleep quality [29].

Protection from UV rays with long-sleeved shirts, hats, and sunglasses, sun avoidance, and utilization of sunscreen with at least 30 sun protecting factors (SPF) is recommended [30].

Future Treatment Options

Remission from SLE is the main goal of treatment while minimizing steroid usage, making early and effective immunosuppressive therapy crucial. Anifrolumab, an interferon type I receptor antagonist, has recently gained approval as a treatment option for extrarenal lupus, marking the first such approval since 2011. For lupus nephritis, newly available options include belimumab (approved by the FDA and EMA) and voclosporin (approved by the FDA). Furthermore, ongoing clinical trials are exploring various substances as potential treatment modalities.[31]

Lupus Nephritis :

The FDA has approved Voclosporin, belonging to the family of calcineurin inhibitors, for treating lupus nephritis based on successful phase Il and Ill trials. When combined with standard mycophenolate therapy, voclosporin showed superiority over standard treatment alone and will serve as an additional therapy option. With its more predictable pharmacokinetics and pharmacodynamics, voclosporin offers potential advantages over existing calcineurin inhibitors, eliminating the need for therapeutic drug monitoring. The long-term use and adoption of voclosporin in lupus nephritis management will depend on further data regarding nephrotoxicity, which is a concern with older calcineurin inhibitors like cyclosporine A. Additionally, voclosporin is expected to be beneficial in managing nonrenal systemic lupus erythematosus (SLE) manifestations, particularly hematologic ones. While controlled trials in nonrenal SLE would be helpful, information on its efficacy in lupus nephritis patients with nonrenal manifestations will accumulate over time.[32]

Trials targeting B-cells via CD19, CD20, and CD22 showed limited success with rituximab and ocrelizumab in lupus nephritis. However, Obinutuzumab, a humanized type II anti-CD20 monoclonal antibody, demonstrated promising results in a phase 2 trial. In this trial, patients with lupus nephritis receiving mycophenolate and corticosteroids were selected at random to get Obinutuzumab 1000 mg or placebo on specific days over a period and followed up to week: 104. Obinutuzumab showed higher complete renal response rates at weeks 52 and 104compared to placebo, along with improvements in other renal response measures, serologies, estimated glomerular filtration rate, and proteinuria, without an increase in serious adverse events, serious infections, or deaths. A phase 3 study for lupus nephritis has completed enrolment, and the non-renal study is underway. [33]

Nonrenal Systemic Lupus Erythematosus :

In addition to nivolumab for nonrenal SLE, several other treatment approaches are undergoing advanced clinical trials.

Janus kinase(JAK) inhibitor :

Janus kinases (JAKs) have an important role in the signaling of various inflammatory cytokines implicated in the pathogenesis of systemic lupus erythematosus (SLE). Additionally, JAK/ STAT signaling pathways are upregulated in lesional cutaneous lupus erythematosus (CLE)skin. Baricitinib, an oral selective and reversible inhibitor of JAK1 and JAK2, has been investigated as a potential treatment for SLE. In a phase 2 placebo-controlled trial involving 314 SLE patients, baricitinib demonstrated superiority over placebo when used in conjunction with standard care in treating arthritis. Baricitinib was under evaluation in two phase 3 SLE trials; however, top-line results prompted the discontinuation of the phase 3 development program for lupus. Nevertheless, a phase 2 study investigating topical ruxolitinib, a JAK inhibitor, for discoid lupus erythematosus (DLE) is currently in progress.[34]

Low Dose IL-2 :

In SLE, the fall of immunological tolerance is a defining feature, possibly stemming from impaired T regulatory cell (Tregs) function and an imbalance between T follicular helper cells and T follicular regulatory cells. Low-dose interleukin-2 treatment in SLE patients has been demonstrated to rebalance T follicular regulatory cells and T follicular helper cells, favoring the former, and has shown clinical effectiveness in managing SLE.[35]

Autologous chimeric antigen receptor (CAR) T-cell therapy :

It has arisen as a hopeful treatment avenue for SLE. CD19+CD20- B cells are connected to the pathogenesis of SLE and CD19-targeted CAR T- cells offer a direct approach to B cell depletion without the need for additional cell types, potentially enhancing efficacy. Preclinical studies in mice have demonstrated encouraging outcomes with CAR T-cells in combating SLE.[36]

DISCUSSION:

The research paper provides a comprehensive overview of treatment change over 2 decades. It highlights the complexity of SLE, which stems from its multifactorial origins, diverse clinical manifestations, and the challenges associated with its diagnosis and management. The paper outlines both older and current therapeutic approaches for managing SLE. Older treatments like corticosteroids, immunosuppressants, and antimalarial drugs have been foundational in controlling inflammation and modulating immune responses. However, the emergence of newer targeted therapies, including biologics such as belimumab, rituximab, Anifrolumab, and voclosporin, has revolutionized SLE management by specifically targeting key pathways implicated in the disease pathogenesis. These biologics offer promising outcomes in terms of reducing disease activity, preventing flares, and improving patient quality of life.

The paper also discusses the importance of non-pharmacologic interventions in managing SLE, such as vitamin D supplementation, dietary modifications, and UV protection. These interventions, alongside pharmacological treatments, play a crucial role in optimizing patient outcomes and reducing disease burden.

Furthermore, the paper delves into potential future treatment options for SLE, including novel biologics targeting B-cell and T-cell pathways, Janus kinase (JAK) inhibitors, low-dose interleukin-2

therapy, and autologous chimeric antigen receptor (CAR) T-cell therapy. These emerging therapies hold promise in further enhancing the standards of living for SLE patients by offering more targeted and effective treatment options.

CONCLUSION:

In conclusion, over the past two decade, there has been a significant improvement in the prognosis for SLE patients. Remedies that are deemed conventional include hydroxychloroquine and glucocorticoids. Severe disease is managed with immunosuppressants which are also employed as steroid-sparing agents. Breakthrough in biological therapies including various monoclonal antibodies directed against B-cell specific molecules, T-cell down-regulation, modulation of signal transduction pathways, etc. will serve as prospective methods of treatment in the future enhancing the standards of living in SLE patients. Overall, the paper underscores the complex nature of SLE and the need for a multidimensional approach to its management. By elucidating the underlying mechanisms driving the disease and exploring innovative therapeutic avenues, researchers and clinicians can continue to advance our understanding and improve outcomes for individuals living with SLE.

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