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Review

State of the art: the treatment of Systemic Lupus Erythematosus

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Abstract

Purpose of the review: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with dysregulated cells in the immune system. The disease affects organs like kidneys, nervous system, joints, and skin. To manage SLE effectively, novel treatments targeting immune system components have been developed. This review investigates the therapeutic potential of existing targeted therapies and explores future innovative approaches for safe, personalized treatment.

Recent findings: SLE treatment involves cytokine targets and specific immunologic pathways, with even small molecules involved.

Summary: the advanced therapeutic options in SLE management give clinicians more tools to control disease activity according to personalized medicine

Keywords

Systemic Lupus Erythematous, immunosuppressive drugs, precision medicine, anti-IFN, anti-B lymphocyte.

Introduction

Systemic lupus erythematosus (SLE) is a multifactor chronic autoimmune disease that primarily affects women of reproductive age (the ratio between females and males

about 8:1 – 15:1), characterized by phases of flare-ups and remission; it can cause severe damage to many organs and tissues [1]. Global SLE incidence and prevalence have surged due to improved diagnostic techniques and international data availability, with North America experiencing the highest incidence due to genetic predisposition, socioeconomic conditions, and environmental factors. [1]. SLE patients' mortality risk is 2.6-fold higher than the general population, primarily due to delayed diagnosis, high disease activity index, infection presence, renal involvement, and major cardiovascular events [2]. According to the classification from the European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) in 2019, an entry criterion for the SLE diagnosis is the presence of at least one positive antinuclear antibody (ANA) test[3], [4]. However, the presence of ANAs is not exclusive to SLE[5], [6], and about 30% of patients with a clinical diagnosis of SLE are ANA-negative[4]. In addition, the diagnosis of SLE requires at least ten additive points accumulated from seven clinical and three immunological domains. The new criteria have been found to have a sensitivity of 96.1% and a specificity of 93.4%[3]. The organs most affected by SLE are the kidneys, nervous system, joints, and skin. Anti-dsDNA, strongly associated with disease activity[7], and anti-extractable nuclear antigen (ENA) antibodies are more specific for SLE diagnosis. Other markers associated with SLE include anti-Sm, U1-ribonucleoprotein, anti-SSA, anti-SSB, anti-histone, anti-ribosomal, and antiphospholipid antibodies [8–12]. Long-term patient management requires regular follow-up and evaluation, with accurate measurement of disease activity challenging due to its complex multisystem features. The most widely used tool is the SLE Disease Activity Index-2K (SLEDAI-2K)[13], the 2004 British Isles Lupus Activity Group (BILAG) index, the Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index (SDI) and the SLE Responder Index (SRI), which integrates criteria from the Safety of Oestrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI, Physician Global Assessment (PGA), and BILAG 2004[14]. The pathogenesis of SLE has been significantly clarified in recent decades, owing to the discovery of dysregulated cells in both the innate and adaptive immune systems. In addition, it has been demonstrated that type-I interferon (IFN) plays a significant role in the hyperactivation of genes encoding pro-inflammatory molecules by target cells; this phenomenon is known as the type-I IFN signature[15]. Although SLE therapy is still based on nonspecific immunomodulatory and immunosuppressive drugs [16], new treatments directed against specific immune system targets have recently been developed, and some have been approved by regulatory agencies[17]. Such new drugs, however, still need to be combined with conventional therapy to achieve acceptable disease control.

This review will discuss the therapeutic potential of available targeted drugs and the future development of novel therapeutic strategies that will lead to safe, personalized therapy, possibly avoiding combination with conventional treatment.

1. Conventional therapy

1.1 Antimalarial drugs

Hydroxychloroquine (HCQ) sulfate, the hydroxylated version of chloroquine, was initially used as an antimalarial agent due to its ability to block plasmodial heme polymerase. Its lipophilic nature allows it to penetrate lysosomes, which are spherical vesicles with hydrolytic enzymes activated by acidic pH. High amounts of alkalinizing HCQ in lysosomes can raise pH, impair lysosome activity and alter metabolic and immune pathways. HCQ inhibits TLR7 and TLR9 signaling and DC maturation, potentially stopping autoantibody production, autophagy, and cross-talk between T and B cells. It should be prescribed to all SLE patients, unless contraindicated, at a target dose of 5mg/kg body weight/day [18]. Individualise treatment depending on the risk of flare and retinal toxicity. Patients with kidney illness, preexisting macular or retinal disease, or tamoxifen usage may require more frequent ophthalmologic monitoring.

1.2 Glucocorticoids

Glucocorticoids (GCs) have been the main treatment for SLE for years, and sparing them is now a target for treating the disease. Patients with moderate-to-severe disease should be dosed based on organ involvement and reduced to a maintenance dose of ≤5 mg/day. Pulses of intravenous methylprednisolone may be considered. Steroids can cause side effects, so steroid-sparing agents can interrupt steroid administration. New therapies are recommended for patients who don't respond to conventional immunosuppressants [18–20]

2. Non-Biological Immunosuppressive

2.1 Azathioprine

Azathioprine is an immunosuppressive medication derived from 6-mercaptopurine, used to induce remission in juvenile acute leukemia. It has a higher therapeutic index and has immunosuppressive effects, including lowering antibody production, extending allograft life, and treating rheumatologic illnesses. AZA decreases T, B, and natural killer cell numbers, as well as cellular and humoral immunity, and suppresses autoantibody production and prostaglandin synthesis. [21][22]

Despite decades of clinical usage, AZA has yet to be established as a first-line therapy for severe SLE. In Lupus Nephritis is most successful when taken as a maintenance or steroid-sparing medication (2-3 mg/kg/day) following remission induction with more solid and faster-acting medicines, such as CYC or MMF. Following the MAINTAIN study, MMF supplanted AZA as the primary therapy for pregnant patients [22]. AZA, on the other hand, has established a niche among mostly female patient groups of

childbearing age since it is one of the few immunosuppressants that are considered safe during pregnancy. Indeed, it is the first-choice medication [23]

It is commonly used in SLE cases without renal involvement when repeated flares occur because of its potential to lower flare frequency. It helps treat severe cutaneous SLE, autoimmune hepatitis, inflammatory bowel disease (IBD), and organ transplants. AZA is also effective as a maintenance treatment in neuropsychiatric SLE and rheumatoid arthritis; however, it is not well tolerated with arthritis [24].

The main adverse effects are Gastrointestinal (12%), leukopenia (28%), and infection (<1%) possibly increased risk of malignancy. There is a risk of severe hematologic toxicity for patients with TPMT and/or NUDIX 15 deficiency; it is recommended to test for these variants before initiating therapy [25–28]

2.2 Methotrexate

Although many potent biological agents have been developed to treat autoimmune inflammatory illnesses, methotrexate (MTX) continues to be one of the most successful and widely used medications [29]

Methotrexate is a well-known competitive inhibitor of dihydrofolate reductase, thereby blocking the regeneration of tetrahydrofolate from dihydrofolate. It is crucial for producing folate cofactors that are necessary for creating new purine and pyrimidine molecules. The effectiveness of methotrexate as an anti-malignant medicine may be primarily attributed to its action method.[30].

The consensus is that the objective of treating SLE should be to effectively manage disease activity and avoid flare-ups by using the smallest feasible amount of glucocorticoids (GCs). To achieve this objective, immunosuppressive agents may help reduce or discontinue the administration of GCs [31]

According to the 2023 update of EULAR recommendation for the management of SLE, for patients who do not show improvement with hydroxychloroquine alone or in combination with glucocorticoids or for patients who are unable to lower their glucocorticoid doses to levels suitable for long-term use, it is recommended to consider adding immunomodulating/immunosuppressive agents such as methotrexate at dose 10-25 mg/week in 1-2 doses (given in one day). It is also indicated as a second-line therapy in active skin disease[18]

2.3 Mycophenolate mofetil

Mycophenolate mofetil (MMF), an immunosuppressive agent, is used to prevent transplant rejection and treat rheumatic illnesses. It suppresses T and B lymphocyte proliferation, reducing immunoglobulin production. MMF is available in formulations like mycophenolic acid (MPA), a prodrug of MMF, and MMF. It is used in moderate to severe disease, LN therapy, and as a steroid-sparing agent. MMF dosage is ≤3000 mg/d in 2 divided doses of mycophenolic acid. Side effects include constipation, diarrhoea, cytopenia, and infections. [32–35]

2.4 Cyclophosphamide

Cyclophosphamide, an immunosuppressant developed in 1958, is primarily metabolized by hepatic cytochrome P450 enzymes to form 4-hydroxy cyclophosphamide and its tautomer aldophosphamide. These metabolites are transported into target cells, inactivating 4-hydroxy cyclophosphamide. Aldophosphamide undergoes spontaneous non-enzymatic β-elimination, forming phosphoramide mustard and acrolein. Phosphoramide mustard chemically modifies DNA by forming interstrand cross-links and preventing DNA replication, triggering apoptosis. This toxic effect on cells dividing, particularly less mature B lymphocytes, decreases antibody generation and reduces the population of circulating effector T cells expressing specific markers.[36]

According to EULAR 2023 recommendations, CYC IV should be considered in patients with organ-threatening or life-threatening disease for the acute treatment of severe autoimmune thrombocytopenia, in patients with active proliferative LN (low-dose, according to Eurolupus biblio) or in at high dose in combination with pulse Intra – venous methylprednisone in patients in patients in high risk of kidney failure due LN

2.5 Tacrolimus

Tacrolimus belongs to the Calcineurin inhibitors agent, which inhibits T-lymphocyte activation. Tacrolimus in SLE has shown promising results in managing various disease manifestations; it improves skin conditions in lupus patients, particularly those with SCLE, DLE, and SLE. It is beneficial in lupus nephritis when combined with other therapeutic agents, especially as a steroid-sparing agent for other organ manifestations. Tacrolimus is a safe and effective treatment option for pure class V (membranous) lupus nephritis, with potential for faster proteinuria resolution and lower lupus flare risk within a year. Its safety profile and tolerability make it a valuable treatment option for individuals with SLE, especially in lupus nephritis cases.

The most common adverse events are nephrotoxicity (40%- 56%) and hypertension

(23% %- 69%). It may be used as part of multimodal LN therapy, often considered when there are contraindications to other agents (e.g., pregnancy). Blood-level monitoring is used to achieve a therapeutic dose and minimize the risk of adverse effects [18, 37–39]

2.6 Ciclosporin

Cyclosporin, an inhibitor of calcineurin, plays a crucial role in suppressing T cell activation and proliferation in SLE, an autoimmune disorder. It prevents the activation and proliferation of T cells, a key component of the adaptive immune system. Cyclosporin reduces disease activity, reducing anti-nuclear antibody and anti-dsDNA antibody titers and improving complement levels and proteinuria. However, it can cause side effects like nephrotoxicity, hypertension, hirsutism, gingival hyperplasia, and viral infection. It is part of multimodal LN therapy and an alternative maintenance therapy. Healthcare providers must closely monitor patients and adjust treatment accordingly. [18, 37, 40]

2.7 Voclosporin

Voclosporin (VCS) is a novel oral calcineurin inhibitor, belonging to the same drug class as tacrolimus and cyclosporine, that inhibits T-lymphocyte activation and proliferation and cytokine production, approved in January 2021 by the FDA at a dosage of 23.7 mg twice daily, for the treatment of active lupus nephritis, in combination with glucocorticoids and conventional immunosuppressive therapy (mycophenolate mofetil/mycophenolic acid)[41, 42]. Two randomized controlled trial (RCT) studies demonstrated improved renal response rate and reduced proteinuria when VCS was added to mycophenolate mofetil (MMF) and steroids, compared with the group receiving MMF and steroids alone[43, 44]. The phase 3 study AURORA 2 assessed the long-term safety, tolerability, and efficacy of voclosporin in patients with lupus nephritis, comparing it to a placebo, over three years of follow-up, focusing on adverse events, biochemical and hematological assessments, and renal response [45]

3. Biological drugs

3.1 Belimumab

Belimumab, a human immunoglobulin G1k monoclonal antibody, was licensed for SLE in 2011 as the first new drug in over 50 years. It targets B-lymphocyte stimulator (BLyS), a cytokine belonging to the TNF superfamily. In a phase III randomized,

placebo-controlled trial, Belimumab showed a decrease in SLE disease activity and sustained improvement in serologic activity. It met the 1-year SRI primary efficacy endpoint and suggested durability of effect until 76 weeks. Addiction to Belimumab should be considered for patients who cannot improve with hydroxychloroquine alone or in combination with glucocorticoids.[18].

3.2 Anifrolumab

Anifrolumab is a fully human IgG1κ monoclonal antibody that targets the type I interferon receptor subunit one and blocks signaling by all type I interferons[46] It was approved in the USA to treat moderate to severe SLE in July 2021[47]. Interferon-Is (IFN-Is) play a significant role in the development of systemic lupus erythematosus (SLE), as shown by genetic information and the link between the IFN-I pathway and disease activity[48]. Anifrolumab 300mg every 4 weeks in moderate to severe SLE reduced disease activity compared with placebo, being well tolerated[49]. Like Belimumab, it was recommended in patients who do not show improvement with hydroxychloroquine alone or in combination with GC or if they cannot lower the GC dose to a long-term, suitable dosage [18].

3.3 Rituximab

It is thought that B lymphocytes play a pivotal role in the pathophysiology of SLE, either directly through the production of cytokines and organ-specific antibodies or through their antigen-presenting ability[50] Rituximab (RTX) is an anti-CD20 chimeric monoclonal antibody (mAb) that acts to promote apoptosis, cell-mediated cytotoxicity, and complement-dependent cytotoxicity, ultimately leading to a decrease in the population of peripheral B cells[51]. Off-label use of RTX in SLE is recommended in cases of organ-threatening or refractory disease, which is defined as a condition that does not respond to various classes of immunosuppressive drugs[18]. In patients affected by refractory SLE, RTX provided up to 73% global response rate, 51% complete remission, and 34% partial remission. Additionally, it significantly reduced proteinuria and SLEDAI and BILAG scores[50]. Despite the widespread use of RTX in SLE, it is unclear what kind of predictive and prognostic factor could influence the patient's response to RTX[52] there are pieces of evidence that early utilization of RTX in SLE could control disease activity, preventing damage caused by oral and intravenous steroids[53].

3.4 Others biologics

Ocrelizumab is an anti-CD20 mAb that binds the same CD20 epitopes of RTX[54]. It

was evaluated in a double-blind, randomized trial in 381 patients affected by severe Lupus Nephritis (LN) that was interrupted due to an adverse event (opportunistic infections)[55]. Nevertheless, It shows some potential in SLE treatment[56]. *Obinutuzumab* is a glycoengineered type-2 CD 20 mAb that has, compared to RTX, a more robust interaction with Fc gamma receptors and a better resistance to internalization. A case series of 9 patients in 6 centers showed the effectiveness and safety of obinutuzumab in SLE refractory to conventional immunosuppressant and RTX. It is under investigation in two controlled trials, REGENCY and ALLEGORY, in renal and non-renal SLE, respectively [57]. *Daratumumab* is a fully humanized anti-CD38 mAb. CD38 is a surface marker more highly expressed in plasmablasts, CD19+ cells, and plasmacytoid dendritic cells of patients affected by SLE [58]. Daratumumab showed excellent clinical and serological response in two patients affected by life-threatening LES. SLEDAI-2K score decreased from a baseline of 21 to 6 after 12 weeks of treatment[59].

Elotuzumab is a humanized monoclonal antibody to cell surface Signaling Lymphocyte Activation Molecule (SLAM) family receptors 7 (SLAMF7), approved in combination with other drugs for the treatment of multiple myeloma[60]. The SLAMF7 were initially identified as NK cell receptors regulating NK cell cytolytic activity, expressed on different types of hematopoietic cells, and play an essential role in immune regulation in health and disease[61]. Researchers analyzed NK cell phenotypes in SLE patients and healthy controls to understand the cytotoxic dysfunction and identify potential therapeutic targets. Elotuzumab is promising since its expression seems altered in systemic lupus erythematosus (SLE) [62].

4 Future therapies for SLE

4.1 Bortezomib: Proteasome inhibition of Survival of Long-Lived Plasma Cells (LLPCs)

Bortezomib is an authorized medication used to treat multiple myeloma (MM). It functions as a proteasome inhibitor. Inhibition of the proteasome leads to the formation of defective immunoglobulin chains, which triggers stress in the endoplasmic reticulum, activates the response to misfolded proteins, and ultimately leads to the death of plasma cells. Additionally, proteasome inhibitors efficiently suppress the generation of pro-inflammatory cytokines by regulating the activation of NF-kB [63]

Bortezomib is a second-line treatment for patients with active refractory systemic lupus erythematosus (SLE) and lupus nephritis (LN), which significantly reduces disease activity. However, it requires close monitoring for potential adverse effects like peripheral neuropathy and hypogammaglobulinemia. A double-blind RCT showed a correlation between bortezomib medication and SLE adverse events, emphasizing the need for careful treatment indications and procedures to prevent adverse events [64].

Recent research on the whole blood transcriptome and expression quantitative trait loci has shown the potential of bortezomib as a promising treatment for systemic lupus erythematosus (SLE) due to its ability to modify the activity of Cathepsin L (CTSL).[65]. A case study has shown that administering lower doses of bortezomib at longer intervals may be advantageous in the treatment of persons with both multiple myeloma and moderately active SLE [66]

4.2 CAR T cells: CD19+ B-cell depletion

CAR T-cells are created by extracting T-cells from a patient's blood and genetically modifying them in a laboratory to express a chimeric antigen receptor (CAR) on their surface. The specific CAR is designed to recognize a particular antigen or protein found on the surface of cancer cells. Once the CAR T-cells are infused back into the patient, they can seek out and destroy the cells that express the target antigen. Mackensen and colleagues used CAR T cells targeted to B lymphocyte CD 19 positive in Five patients with SLE refractory to several immunosuppressive drug treatments. Patients, after lymphodepletion, received their autologous T cells transduced with a lentiviral anti-CD19 CAR vector. All five patients also reached remission after the B cell's naive appearance. Hence, the CAR T cells approach could be used in SLE patients with refractory disease [67]

4.3 BDCA2: Anti-pDC antibody

BIIB059 is a humanized IgG1 monoclonal antibody that binds to blood DC antigen 2 (BDCA2), found on plasmacytoid dendritic cells (pDCs). These cells produce IFN-1 and are the primary source of IFN-1 in response to immune complexes. In SLE, pDCs diminish in the bloodstream and accumulate in damaged organs, making them an attractive target for therapeutic intervention. BIIB059's administration has shown positive safety, pharmacokinetic/pharmacodynamic characteristics, and biological effectiveness. [68]

4.4: Treg enhancement

The therapeutic effectiveness of a specific subset of regulatory T (Treg) cells, identified by the presence of the FOXP3+ marker and their ability to inhibit the immune system, has been shown in preclinical models of SLE[69]. In a thrilling period in the field of gene and cell therapy, characterized by a multitude of innovative techniques and tactics that are enhancing the development of Treg cell-based immunotherapies, ensuring the optimal equilibrium between immunosuppression and immune surveillance will be crucial for achieving success in the development of Treg cell-based therapeutics as a kind of immunotherapy [70]

4.5 JAK inhibitors: Type-I and type-II IFN signaling inhibition

The JAK-STAT mechanism is crucial for cell proliferation, differentiation, maturation, activation, migration, and survival across almost all cell types. ILs, IFNs, colony-stimulating, and growth factors bind to non-enzymatic receptors (Type I/II). When cytokine receptors are activated, JAK enzymes cross-phosphorylate each other and phosphorylate tyrosine residues in the cytoplasmic domains, creating binding sites for STAT family DNA binding proteins. Activated STATs undergo tyrosine phosphorylation, forming homo- or hetero-STAT-dimers that trigger gene transcription in the nucleus. Type I and II interferons and cytokines contribute to SLE pathogenesis. Genome-wide association studies (GWAS) have revealed STATs as vulnerable genes in SLE, so the JAK-STAT is an exciting pathway to consider for SLE therapy [71]

Tofacitinib, a JAK1/3 inhibitor, is approved for treating rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. It improves cardiometabolic and immunologic markers linked to SLE accelerated atherosclerosis, enhances HDL cholesterol levels, and improves arterial stiffness. The Phase 1 randomized safety trial showed safety and tolerability, with some benefits more significant in STAT4 risk allele carriers. [72]

Ruxolitinib, a small-molecule inhibitor targeting JAK1/2, effectively treats immunologic skin disorders like alopecia areata and improves cutaneous lesions in lupus models. However, systemic use of oral JAK inhibitors for cutaneous lupus erythematosus (CLE) is limited due to side effects. Topical JAK inhibitors may be a viable treatment option.[73]

5. Conclusions

SLE management is challenging for clinicians and patients due to its tortuous evolution and potential therapy damage. Modern medicine aims for clinical remission or minimal disease activity using targeted therapies and sparing corticosteroid use. It's mandatory to choose drugs suitable for pregnancy in females of childbearing age.

Lupus can be effectively managed through a multi-pronged treatment strategy involving immunosuppressant drugs and targeted biologics. This approach addresses the autoimmune and inflammatory components of the disease, improving clinical outcomes and quality of life. However, further research is needed to fully understand

and manage this complex autoimmune disorder. A multidisciplinary approach involving rheumatologists, nephrologists, dermatologists, and other healthcare professionals is crucial for successful treatment. The review emphasizes the significance of a personalized, multidisciplinary approach to lupus therapy, backed by ongoing research, to provide effective and tailored management strategies for this challenging autoimmune condition.

- SLE treatment involves cytokine targets and specific immunologic pathways, with even small molecules involved
- the advanced therapeutic options in SLE management give clinicians more tools to control disease activity according to personalized medicine
- To manage SLE effectively, novel treatments targeting immune system components have been developed

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Declarations

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GC: Conceptualization, Writing-original draft, Writing-review & editing.
AGL: Conceptualization, Writing-original draft, Writing-review & editing.
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The authors declare that they have no conflicts of interest.

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