Journal of High School Science

Novel cellular engineered therapeutics targeting autoreactive B cells in Systemic Lupus Erythematosus

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Submitted: January 9, 2025, Revised: version 1, March 8, 2025, version 2, March 22, 2025
Accepted: March 31, 2025

Abstract

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disorder affecting millions of patients worldwide; it is characterized by dysregulated B cells attacking healthy tissues. Current treatments are limited in their efficacy and often come with significant side effects, such as increased infection risk. Recent advancements in targeted therapies offer potential new treatment avenues by addressing specific immune pathways involved in SLE. This review explores the immunology of SLE, the role of immune dysregulation in its pathogenesis, and the current treatment landscape, highlighting the emerging potential of novel therapies such as CAR T-cell therapies, anifrolumab, belimumab, and bispecific T-cell activators. Although promising, these new therapies present challenges, including long-term efficacy and safety concerns, underscoring the need for further research to optimize treatment strategies and improve patient outcomes. A CAR T-cell therapy is proposed which uses genetically engineered CAR expressing allogeneic T cells; partly derived from cryopreserved leukapheresis products of patients with SLE; that are programmed to recognize and bind to surface markers CD11c, CD86 and CD40L, which are overexpressed in SLE patients, and uniquely found on autoreactive B cells. By focusing on these specific markers, the proposed therapy aims to reduce disease progression while avoiding the depletion of non-autoreactive B cells, thus minimizing adverse effects.

Keywords

Lupus, Autoimmune disorder, Cell therapy, Inflammation, Lymphocytes, Autoreactive B cells, CAR T-cell, Autoantibodies, Immunosuppressant

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https://doi.org/10.64336/001c.133840

Introduction

SLE is a chronic autoimmune disease where the immune system mistakenly attacks healthy tissues, causing inflammation and damage to various organs, including the kidneys, skin, joints, and heart. Ordinarily, specialized immune cells called B cells produce antibodies to target foreign pathogens and prevent illness. In this disease, the B cells produce antibodies that target self-antigens, leading to an ongoing inflammatory response against healthy tissue rather than invasive microbes. This immune dysfunction can result in symptoms such as fatigue, joint pain, and skin rashes, though the severity and presentation of symptoms can vary widely between individuals (1).

Epidemiologically, SLE disproportionately affects women. The prevalence of SLE in the U.S. is estimated at 72.8 per 100,000 person-years, with women being nine times more likely to be affected than men. The disease is more common among certain racial and ethnic groups, with the highest prevalence observed in Native American women (270.6 per 100,000), followed by Black women (230.9 per 100,000), Hispanic women (120.7 per 100,000), and White women (84.7 per 100,000). In 2018, approximately 204,295 individuals in the U.S. were diagnosed with SLE, highlighting the significant public health impact of this autoimmune disorder (2).

The exact causes of lupus remain unclear, but it is widely believed that genetic, environmental, and hormonal factors contribute to its development. Estrogen, in particular, is thought to be a significant factor in the higher prevalence of lupus among women. Animal studies have demonstrated that estrogen can increase the survival of autoreactive B cells, which produce the autoantibodies that cause damage when a person has SLE. In humans, estrogen also influences the immune system by increasing the expression of CD40L on T cells, which can promote immune activation and inflammation. Furthermore, estrogen binds to estrogen receptors (ER) on immune cells, controlling gene expression in ways that can promote autoimmunity. For example, estrogen receptor α (ERα) has been implicated in the development of autoreactive B cells (1).

Despite significant progress in understanding the pathogenesis of SLE, there remains no cure, and current treatment options primarily aim to control symptoms and prevent organ damage. This highlights the need for continued research into the molecular mechanisms of lupus and the development of more targeted therapies that can better manage the disease and improve patient outcomes. Fortunately, several modern technologies have been created that shift the paradigm of what is possible in biology research and therapeutic development. Many of these may improve our understanding and treatment of SLE. This review discusses the immunology of SLE, its pathology, current treatments on the market for SLE, and a novel proposed cell therapy for SLE.

Immunology of Lupus

Important aspects of the immune response of SLE, such as B cells, T cells, antibodies, and autoreactivity, play significant roles in the pathophysiology of SLE. Understanding their dysfunction is crucial for comprehending the disease and advancing its treatments.

B cells produce antibodies that bind to specific antigens. In SLE, these cells become dysregulated, producing autoantibodies that

target the body's tissues. These autoantibodies form immune complexes with self-antigens, which can deposit in organs like the kidneys, triggering inflammation and tissue damage. Beyond antibody production, B cells also regulate immune responses by influencing other immune cells through cytokine secretion and receptor interactions. Cytokines are tiny protein messengers that bind to immune cell receptors to alter their activity. Dysfunctional B cell activation, particularly when driven by cytokines produced by CD4+ helper T cells, has been implicated in the development and progression of SLE (3).

Antibodies, essential components of the immune defense, can neutralize pathogens or mediate immune cell functions. In SLE, however, the production of autoantibodies is a major part of the disease. These autoantibodies, such as anti-dsDNA, bind to nucleic acids released from damaged cells, forming immune complexes. These complexes can activate the complement system, a series of proteins that amplify inflammatory responses and tissue injury. Additionally, autoantibodies can interfere with the clearance of dead cells and cellular debris, continuing immune activation and further tissue damage (4). Neutrophil extracellular traps (NETs), which are web-like structures of DNA and proteins released by neutrophils, contribute to this process by providing a source of autoantigens that fuel the cycle of inflammation and immune dysregulation in SLE (5).

T cells also play a major role in SLE. These cells include CD4+ T cells, which activate B cells to produce antibodies, and CD8+ cytotoxic T cells, which kill infected or defective cells. Regulatory T cells (Tregs) normally suppress immune responses to maintain tolerance to self-antigens. In SLE, however, Tregs often fail to function effectively, allowing autoreactive immune responses to persist. This loss of tolerance contributes to the unchecked activation of autoreactive T and B cells, fueling the autoimmune process (6).

Self-tolerance is a process that normally eliminates autoreactive immune cells during their development. Autoreactive B and T cells, which target the body's own cells, survive and multiply in some patients because this tolerance mechanism is defective. Naturally occurring autoantibodies (NAbs) are part of the immune system's normal function, helping clear dead cells and debris. However, in SLE, these autoantibodies become dysregulated, leading to harmful immune responses instead of protective ones. This imbalance highlights the thin boundary between helpful and harmful immune activity in autoimmune diseases like SLE (7).

Several mechanisms drive the pathogenesis of SLE. The formation of immune complexes, made of autoantibodies and antigens, triggers the activation of the complement cascade, leading to tissue damage and inflammation (4, 7). An imbalance in pro-inflammatory and anti-inflammatory cytokines exacerbates immune dysregulation, amplifying the disease’s progression (6). Furthermore, interactions between autoreactive B and T cells intensify immune activation through processes like T cell-dependent B cell activation, further driving the production of pathogenic autoantibodies (3, 6). These mechanisms collectively illustrate the complexity of SLE and its reliance on intricate immune system dynamics. By targeting these

pathways, therapies aim to restore immune tolerance and mitigate the damaging effects of autoimmunity (7).

Current treatments for Lupus

Currently, SLE treatment revolves around managing symptoms, reducing inflammation, and preventing organ damage. Glucocorticoids (GCs) are commonly used to treat SLE because they quickly reduce disease activity. GCs decrease cytokine production, prevent white blood cells from traveling to areas of inflammation, and alter the function of immune and endothelial cells. These medications are used by up to 88% of SLE patients, many of whom need long-term treatment. However, long-term use of GCs can lead to serious side effects like organ damage, which can affect survival rates. To avoid these risks, doctors aim to limit GC use based on disease activity and treatment goals. High doses of GCs, such as methylprednisolone, provide fast relief from flares and are 10–15 times more potent in activating the glucocorticoid receptor pathway. However, doses above 30–100 mg/day of prednisone, a synthetic GC that mimics the action of cortisol, can lead to long-term problems, such as osteoporosis and heart disease (8).

These limitations clearly indicate that a change is necessary for SLE treatments. For long-term treatment, lower doses (less than 5 mg/day) of GCs are preferred, especially when combined with other drugs that help maintain remission without causing side effects. Doctors usually stop GC treatment after patients have been in remission for about five years to reduce the risk of flare-ups. Gradually decreasing GC doses has been shown to prevent flares and reduce long-term damage (8).

Other immunosuppressive drugs like cyclophosphamide (CYC), mycophenolate mofetil (MMF), and azathioprine (AZA) are also treatments for SLE because they target different B-cell populations that play a role in it. CYC works by depleting proliferating cells, including B cells, and is often combined with GCs. It is particularly effective for severe cases of lupus nephritis (LN), a common symptom of SLE in which the kidneys inflame and are attacked by the body's own immune cells. MMF is an oral prodrug metabolized to mycophenolic acid, which inhibits DNA synthesis in T and B cells, making it effective in promoting remission in SLE patients with LN. MMF is preferred over CYC for long-term therapy due to less severe side effects and better outcomes. AZA inhibits DNA replication and is less potent than MMF, often resulting in higher rates of symptom recurrence. It is used primarily for the maintenance of remission of SLE (8).

These current treatments prove that there are effective methods to manage SLE symptoms; however, the use of immunosuppressants carries significant risks. They reduce the functionality of T cells, B cells, and various innate immune cells, such as neutrophils and macrophages, making it harder for the body to detect and eliminate pathogens. Immunosuppressive therapies contribute to heightened infection risks by compromising the immune system's ability to respond to common pathogens (9). The balance between managing disease activity and minimizing infection risk is critical in SLE treatment.

The two types of treatments for SLE can be classified as broad or targeted. Broad therapies, such as glucocorticoids and

immunosuppressants, broadly suppress immune activity but come with significant side effects, including infection risk and organ damage. Targeted therapies, on the other hand, focus on specific immune pathways or cell populations. These include antimalarials and NSAIDs for symptom management, JAK-STAT and mTOR inhibitors for modulating immune signaling, and more advanced approaches like CAR T cells and BiTE antibodies, which selectively target B cells. While targeted therapies offer greater precision, challenges such as long-term efficacy, safety, and accessibility remain.

CAR T cell therapies, which genetically engineer T cells to target specific antigens, have shown promise in treating autoimmune diseases. CAR T treatments targeting CD19, a B cell marker, have demonstrated effective B cell depletion in hematologic cancers. A new CD19-CAR T product, CABA-201, developed with a fully human CD19 binder, has been tested in patients with autoimmune diseases (including SLE) that do not respond well to other treatments. In preclinical studies, CABA-201 demonstrated similar potency to existing CAR T products while showing no off-target cytotoxicity. Clinical data from patients suggest that CABA-201 CAR T cells can become activated and eliminate CD19 B cells, offering a potential new treatment option that could allow patients to have drug-free remissions, especially in those who have not responded well to conventional therapies (10).

Anifrolumab is a monoclonal antibody designed to block type-1 interferon (IFN) cytokine signaling, which plays a significant role in the inflammation associated with SLE. It binds specifically to subunit 1 of the IFN receptor (IFNAR1), preventing the formation of the IFN/IFNAR complex, which is responsible for triggering inflammation in lupus. Clinical trials have demonstrated that anifrolumab can significantly reduce levels of anti-dsDNA antibodies and improve immune markers, including complement levels, in patients with increased type-1 interferon levels. Anifrolumab is associated with several risks, such as increased susceptibility to infections like respiratory infections and herpes zoster, as well as hypersensitivity reactions, including anaphylaxis. Furthermore, its benefits often do not last long, as the immune system tends to recover once treatment is discontinued, potentially leading to the recurrence of symptoms if type-1 IFN activity remains high (11).

Another commonly used treatment for SLE is belimumab, a monoclonal antibody that targets B-cell activating factor (BAFF), which is essential for the survival and function of B cells. By inhibiting BAFF, belimumab reduces the number of B cells involved in the autoimmune response, which can alleviate symptoms of SLE, such as disease flares and high levels of harmful antibodies. In a large cohort study in Spain, belimumab was shown to help many patients achieve fewer flare-ups, improved immune markers, and even the ability to stop using steroids, which are often associated with severe side effects. However, belimumab is also linked to immune-related adverse events, including an increased risk of infections, nausea, and gastrointestinal issues. Discontinuing belimumab can lead to a recurrence of SLE symptoms, which suggests that long-term use may be necessary to maintain its benefits (12).

CD19/BAFF-R dual-targeted CAR T cells are a form of immunotherapy designed to treat B-cell malignancies, including acute lymphoblastic leukemia, by targeting two distinct antigens: CD19 and BAFF-R. They are currently in a clinical trial for autoimmune diseases, including SLE. The CD19-BAFF CAR T cells have been optimized to overcome the challenge of antigen escape, which can occur when cancer cells lose the target antigen, such as CD19, during treatment. The dual targeting approach increases the effectiveness of the therapy, allowing for broader tumor recognition and elimination, even in the presence of cells that have lost either CD19 or BAFF-R expression. The treatment also can prolong *in vivo* persistence, suggesting that it may lead to long-lasting remissions. However, while promising, there are some drawbacks to this approach. The complexity of designing bispecific CAR constructs can lead to challenges in ensuring that both antigens are targeted effectively, and the therapy's applicability in diseases like SLE remains to be fully explored. In SLE, targeting both CD19 and BAFF-R could potentially reduce B-cell activity and regulate the immune system more effectively, but there still is not enough research to support this (13).

A novel treatment under testing for its effectiveness in treating SLE is CLN-978, a bispecific T-cell activator that targets both B cells and T cells to treat autoimmune diseases. CLN-978 works by binding to CD19 on B cells and CD3 on T cells, redirecting the immune system to target and eliminate B cells that drive the autoimmune response in lupus. This bispecific approach has the potential to overcome some of the challenges faced by traditional therapies, such as targeting B cells with low CD19 expression, which are difficult to treat with conventional therapies. Furthermore, CLN-978 is designed to have a longer circulation time in the bloodstream, reducing the need for frequent infusions and potentially lowering toxicity. The treatment is administered subcutaneously, making it a more patient-friendly option compared to intravenous therapies. Although promising, CLN-978's ability to eliminate both pathogenic and healthy B cells could pose risks, as it may disrupt normal immune function. However, its innovative approach offers a potentially new treatment avenue for lupus patients who have not responded to existing therapies (14).

DESCARTES-08 is an innovative mRNA-engineered CAR T-cell therapy designed by Cartesian Therapeutics for treating autoimmune diseases such as myasthenia gravis (MG) and SLE. Unlike conventional CAR T-cell therapies, which rely on DNA engineering and often require preconditioning chemotherapy, DESCARTES-08 uses mRNA to transiently modify T cells to target B-cell maturation antigen (BCMA) on plasma cells. This approach avoids the risks of genomic integration and eliminates the need for suppressing lymphocyte response, making it safer for outpatient administration. In a Phase 1b/2a trial for MG, DESCARTES-08 was well-tolerated, with no dose-limiting toxicities, cytokine release syndrome, or neurotoxicity reported. Clinical improvements on MG severity scales exceeded clinically meaningful thresholds and persisted for up to nine months. However, a limitation is the lack of data on long-term effectiveness, as the follow-up period was only nine months. Additionally, the therapy may not provide lasting remission because mRNA-modified cells are designed to

be temporary and do not persist long-term in the body (15). Further investigation is needed to confirm its efficacy and safety for different patient populations.

Antimalarials, primarily hydroxychloroquine (HCQ), are effective treatments for SLE due to their immunomodulatory and anti-inflammatory properties. These drugs help prevent disease flares by reducing immune system hyperactivity and have been shown to decrease long-term organ damage and mortality rates. Furthermore, HCQ use is associated with lower infection risks, including protection against herpes zoster and *Pneumocystis jirovecii*, and may reduce the likelihood of preeclampsia in pregnant SLE patients. However, antimalarials can come with dangerous side effects: retinal damage, gastrointestinal disturbances, and skin reactions. Despite these risks, HCQ toxicity is rare, especially at the commonly prescribed 200 mg/day dose. Unfortunately, many SLE patients do not take HCQ consistently, either due to under-prescription by physicians or concerns about side effects (16).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of medications commonly used to manage pain, inflammation, and fever by inhibiting cyclooxygenase enzymes, which play a key role in prostaglandin production. In SLE, NSAIDs are often prescribed to alleviate symptoms like joint pain, muscle aches, and mild pleurisy, making them beneficial for patients with musculoskeletal symptoms. Their advantages include rapid symptom relief and widespread availability, but they do not address the underlying autoimmune mechanisms driving SLE. NSAID use also carries notable risks, including gastrointestinal irritation, kidney dysfunction, and an increased risk of cardiovascular events, which can be especially concerning for SLE patients already predisposed to these complications. While NSAIDs can provide symptomatic relief and manage discomfort, they do not alter the progression of lupus itself (17).

JAK-STAT inhibitors are small molecules that target the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways. These pathways are abnormally activated in SLE and contribute to organ damage. These inhibitors work by blocking multiple cytokine signals involved in lupus pathogenesis. While JAK inhibitors like tofacitinib, baricitinib, and deucravacitinib have not yet been approved for SLE, clinical trials suggest they could be beneficial. Tofacitinib has been shown to improve vascular function, reduce the type I interferon signature, and decrease NET formation, while baricitinib demonstrated efficacy in treating lupus rash and arthritis in some trials but failed to replicate results consistently. Deucravacitinib, a selective TYK2 inhibitor, has shown promise in phase 2 trials and is being investigated further. However, safety concerns remain a major drawback, as JAK inhibitors have been linked to increased cardiovascular risk, venous thromboembolism, and potential malignancies in patients with other autoimmune diseases, raising concerns given SLE patients' already heightened cardiovascular risk (18).

Mammalian target of rapamycin (mTOR) inhibitors are a class of drugs that target the mTOR, a central regulator of cell growth, metabolism, and immune function. In the

context of SLE, mTOR signaling is abnormally activated, contributing to excessive immune cell proliferation, impaired autophagy, and increased production of inflammatory cytokines. By inhibiting mTOR, these drugs help restore immune homeostasis, reduce disease activity, and potentially decrease reliance on corticosteroids. Clinical trials have demonstrated promising efficacy, with patients experiencing fewer disease flares and improved immune regulation. However, mTOR inhibitors cause side effects such as metabolic disturbances, mucositis, and increased infection risk due to their immunosuppressive nature. Despite these challenges, the growing body of research suggests that mTOR inhibitors offer a viable targeted therapy for SLE, providing an alternative to conventional broad-spectrum immunosuppressants. Further studies with larger patient populations are needed to fully establish their long-term safety and optimal use in precision medicine approaches for SLE treatment (19).

A bispecific T-cell engager (BiTE) is a type of antibody designed to target two distinct antigens simultaneously, typically involving one part that binds to a T-cell receptor and another that binds to a target cell, such as a tumor cell or an immune cell. This dual binding redirects the immune system's T-cells to attack the target cells, leading to immune-mediated destruction. Blinatumomab, a specific BiTE, is designed to target CD19 on B-cells and CD3 on T-cells, making it useful for autoimmune diseases like SLE. By targeting and eliminating B-cells, blinatumomab helps to reduce autoantibody production and potentially improve disease outcomes. The benefits of blinatumomab include its ability to precisely target B-cells without broadly suppressing the immune system, which reduces the risk of infections compared to traditional immunosuppressive therapies. However, there are potential side effects such as cytokine release syndrome, neurological symptoms, and challenges related to its long-term safety and effectiveness in treating a chronic disease like SLE (20).

Table 1. A comparison of treatments for SLE

Categories	Examples	Limitations
Antibodies	Anifrolumab, Belimumab	Increased risk of infections, limited long-term efficacy
Antimalarials	Hydroxychloroquine (HCQ)	Retinal damage, gastrointestinal disturbances, skin reactions
Bispecific T-cell engager	CLN-978, Blinatumomab (BiTE)	Potential for broad B cell depletion, unknown long-term effects
DNA-modified CAR T	CABA-201, CD19/BAFF-R dual-targeted CAR T cells	Risk of cytokine release syndrome, potential for off-target effects
Immunosuppressants	Cyclophosphamide (CYC), Mycophenolate mofetil (MMF), Azathioprine (AZA)	Increased risk of infections, potential for long-term toxicity
JAK-STAT Inhibitors	Tofacitinib, Baricitinib, Deucravacitinib	Increased cardiovascular risk, venous thromboembolism, potential malignancies, safety concerns

Proposed treatment

Current treatments for SLE typically use broad immunosuppression to eliminate as many B cells as possible. However, this also eliminates B cells that are functioning properly to prevent infections. Therefore, broad therapies can induce dangerous side effects, such as increasing the rate of infection. To address this limitation, a bispecific chimeric antigen receptor (CAR) T-cell therapy designed to specifically target and destroy autoreactive B cells based on their surface markers while sparing healthy ones would provide a more precise and effective treatment option for SLE patients.

The proposed therapy works by using genetically engineered allogeneic T cells that express CARs that are programmed to recognize and bind to surface markers that are overexpressed when a patient has SLE or uniquely found on autoreactive B cells. These markers include CD11c, CD86, and CD40L. CD11c B cells contain increased T-bet in lupus patients, and when these cells are eliminated, the disease is found to be alleviated in mice (21). CD86 is a marker found on B cells that, when increased, allows the B cell to produce more CD80 and, as a result, leads to a stronger immune response in SLE (22). The increased expression of CD40L in B cells can contribute to the production of autoantibodies associated with SLE, and blocking CD40L activity significantly reduces the production of these pathogenic autoantibodies (23). By focusing on these specific markers, the proposed therapy aims to reduce disease progression while avoiding the depletion of non-autoreactive B cells and minimizing adverse effects.

To identify CD11c, CD86, T-bet, and CD40L on CD19 expressing B cells, researchers could isolate peripheral blood mononuclear cells (PBMCs) from SLE patients and healthy controls, then use flow cytometry to analyze cells stained with antibodies for each marker. Before staining, cells are incubated with anti-CD16/CD32 to block Fc receptors and reduce nonspecific binding (22). Advanced equipment, like Fortessa2 and LSR-II cytometers, helps measure the percentage of these cells, and FlowJo or other cell gating software ensures that the identification of the cells is accurate by only examining the signal of the CD19+ B cells (21, 22, 23). If there is expression detected on the B cells, the patient might be eligible for this type of therapy.

Patient selection for the bispecific CAR T-cell therapy would prioritize individuals with SLE whose symptoms persist despite using conventional treatments on the market and exhibit signs of autoreactive B-cell activity. Diagnostic criteria would include elevated levels of CD11c, CD86, or CD40L B cells, identified through advanced techniques such as flow cytometry or sequencing. Additional factors, like high levels of autoantibodies or symptoms such as lupus nephritis, would also be noted. During early-phase trials, baseline evaluations of these markers would help group patients and measure therapeutic outcomes effectively.

Testing the therapy would follow a structured clinical trial pathway. Phase I trials would focus on safety and determining the optimal dosage in a small group of lupus patients, monitoring for side effects like cytokine release syndrome, and assessing how effectively the therapy targets and eliminates autoreactive B

cells without affecting healthy ones. This assessment could be done by running the same flow cytometry panel that was used to assess eligibility on PBMC samples after each round of treatment. Decreases in the levels of CD11c, CD86, and CD40L on B cells would indicate that the treatment is properly targeting those populations. Phase II trials would involve a larger patient group to assess the effectiveness of the treatment and analyze decreases in autoantibody levels. This analysis is critical, as it would indicate whether the therapy is effective at eliminating autoreactive B cell responses. Patients' symptoms would be monitored throughout to determine whether decreased autoantibody levels correlated with improved quality of life. Phase III trials would focus on confirming the therapy's safety and effectiveness across a larger, more diverse group of lupus patients. These trials would also help narrow down criteria for selecting patients who are most likely to benefit from the therapy and establish protocols for long-term monitoring of outcomes and potential side effects.

One major concern is off-target effects, as the markers CD11c, CD86, and CD40L can be present in small amounts on normal B cells and other immune cells. This could lead to unintended interference with normal immune function. Patients would be carefully tracked to determine if they are experiencing infections at higher rates than the untreated groups during Phase I-III trials. Another challenge is immune escape, where autoreactive B cells might adapt by downregulating the expression of these markers, making the treatment less effective over time. To counter this, the therapy could be used in combination with other treatments that eliminate autoreactive B cells through a different mechanism if the patient is no longer getting positive results through the treatment alone. Additionally, since the therapy involves using allogeneic T cells, there is a risk of graft-versus-host disease (GVHD), where the donor T cells attack the patient's healthy tissues. However, in this context, it is important to note that CAR-T cells, obtained from cryopreserved leukapheresis products of patients with SLE, despite their prior treatment with immunosuppressive therapies and targeting the B19 antigen, were less likely to produce inflammatory cytokines and ICANS responses. These allogeneic products may show an advancement over autologous products (24). These potential issues highlight the importance of thorough testing during preclinical and clinical trials to ensure both the safety and effectiveness of the therapy for patients with SLE.

In summation, a bispecific CAR T-cell therapy has the potential to be an effective lupus treatment by selectively targeting autoreactive B cells through markers such as CD11c, CD86, and CD40L. This approach could provide better outcomes with reduced side effects compared to traditional therapies.

Discussion

Current therapies for SLE, including GCs and immunosuppressants, underscore the delicate balance between managing disease activity and minimizing long-term side effects. While GCs can be effective in quickly managing symptoms, their use is accompanied by significant risks, such as organ damage and heightened susceptibility to infections (8). Similarly, immunosuppressants like MMF and CYC offer efficacy but contribute to compromised immune function (9). These

findings reinforce the necessity for more targeted therapies that reduce disease activity without excessive immune suppression.

Emerging therapies, such as CAR T-cell treatments (CABA-201) and monoclonal antibodies like anifrolumab and belimumab, demonstrate significant progress toward precision in treating SLE. CAR T cells provide an innovative approach by offering potential drug-free remission through targeted B-cell depletion (10). Dual-targeted CD19/BAFF-R CAR T cells may improve B-cell depletion and prevent antigen escape, but their efficacy in SLE is still under investigation (13). The risks of prolonged immune suppression and cytokine release syndrome must be considered in future research.

Anifrolumab blocks the type-1 IFN pathway, a key driver of SLE. However, its benefits are limited by its short-term effectiveness and potential safety risks (11). The success of these therapies highlights the importance of understanding disease-specific immune dysregulation and tailoring treatments accordingly.

Antimalarials, such as HCQ, remain a widely used SLE treatment due to their immunomodulatory effects, which reduce disease flares and long-term organ damage (16). Though useful for symptom relief, NSAIDs do not modify disease progression and pose risks, such as gastrointestinal and cardiovascular complications (17).

JAK-STAT inhibitors target key inflammatory pathways in SLE and have shown promise in early trials, though concerns regarding cardiovascular risk remain (Nikolopoulos & Parodis, 2023). mTOR inhibitors help restore immune balance by reducing excessive immune activation, but metabolic disturbances and infection risks limit their widespread use (9).

BiTE antibodies, such as blinatumomab, offer precise elimination of B cells, reducing autoantibody production while avoiding broad immunosuppression, though there are risks associated, such as cytokine release syndrome (20). The development of bispecific therapies, such as CLN-978, marks a promising frontier in SLE treatment. The use of an antibody rather than a cell therapy results in significant cost savings to the patient. Moreover, the subcutaneous administration of CLN-978 could enhance patient convenience and adherence (3).

Despite advancements, several challenges persist. For example, the need for long-term administration of therapies like belimumab to prevent relapse raises concerns about patient compliance and cost-effectiveness (12). Additionally, the recurrence of symptoms after discontinuation of targeted therapies emphasizes the chronic nature of SLE and the need for a treatment that provides long-term regulation of the immune system.

Another limitation lies in the generalizability of findings from clinical trials to diverse populations. Given the significant racial and ethnic disparities in SLE prevalence and severity, it is crucial to evaluate whether these emerging therapies provide equitable benefits across all patient groups (2). Future studies must prioritize inclusivity to address this gap by prioritizing diverse recruitment in their clinical trials. Affordability of treatments is an

ongoing issue that must be addressed as well to ensure patient access.

Given the limited success of iPSC-derived therapies, including clinical trials such as Fate Therapeutics' FT819, which is still in early-phase development, adult immune cells are preferred over iPSCs (25). iPSCs have not yet yielded FDA-approved immunotherapies due to concerns over their maturity and functionality (26). While iPSC-based products like FT819 show promise, their reliance on less mature cells may hinder their therapeutic efficacy compared to adult cell-derived therapies. More mature, functional immune cells have already demonstrated clinical success in trials such as Poseida's CAR T-cell therapy P-BCMA-ALLO1 (27).

The development of bispecific therapies, such as CLN-978, marks a promising frontier in SLE treatment. The use of an antibody rather than a cell therapy results in significant cost savings to the patient. Moreover, the subcutaneous administration of CLN-978 could enhance patient convenience and adherence (3). Future research should focus on optimizing the safety and long-term efficacy of these treatments while exploring their use in combination with existing therapies.

One proposed approach that could overcome current limitations is a bispecific CAR T-cell therapy designed to selectively target autoreactive B cells while sparing healthy B cells, thereby reducing the risk of infection. This therapy focuses on overexpressed markers, such as CD11c, CD86, and CD40L, that are found on autoreactive B cells in SLE patients. By using genetically engineered T cells that recognize and eliminate these specific B cells, the therapy aims to alleviate disease progression without inducing widespread immunosuppression or damaging normal immune function. This approach has the potential to offer more precise treatment with fewer side effects compared to traditional therapies.

Alongside new therapies, understanding the molecular and genetic causes of SLE is crucial. Tools like CRISPR and single-cell sequencing could help find new treatment targets and make care more personalized. Such approaches could lead to interventions that restore immune tolerance rather than merely suppressing immune activation.

Conclusion

Systemic lupus erythematosus is characterized by a sub population of dysregulated B cells which attack healthy tissues. Immunosuppressants, anti-inflammatory agents and pain relievers comprise the mainstay of conventional palliative medicine but are accompanied by heightened risk of pathogen infection, organ toxicity and the risk of relapse, which can only be avoided with continued – often lifetime – use.

Emerging therapies, such as antibodies, CAR T-cells and their iterations, specifically target autoreactive B cells, thereby preserving immune function. CAR T-cells – which are effectively 'living drugs' typically are only administered once and do away with the need for chronic lifetime administration. These newer therapies are however disadvantageous, in terms of requiring initial immunodepletion (for CAR T-cells), causing aberrant cytokine release, causing immune escape by increasing selective pressure, promoting secondary

malignancies, non generalizability for diverse populations, patient compliance and cost-effectiveness.

To minimize some of the above mentioned adverse effects and disadvantages, bispecific allogenic CAR T-cells; partly sourced from cryopreserved leukapheresis products of patients with SLE therapy; will be engineered to target multiple overexpressed markers such as CD11c, CD86, and CD40L on autoreactive B cells. The proposed therapy hence may remove the requirement for initial immunodepletion, may decrease the incidence of GVHD and cytokine release, and decrease the incidence of immune escape. This approach has the potential to offer more precise treatment with fewer side effects compared to traditional therapies.

While significant strides have been made in understanding and managing SLE, this review highlights the ongoing challenges in balancing efficacy, safety, and accessibility of treatments. Emerging therapies hold promise for transforming SLE care, but their limitations emphasize the need for continued research into disease mechanisms and innovative approaches. One such approach is proposed in this paper. By integrating advances in immunology and biotechnology, the future of SLE treatment may shift from disease management toward durable remission and improved quality of life for patients.

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