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Review

In the Pursuit of Precision: Novel Target Therapies Revolutionizing SLE Care

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Abstract: Systemic lupus erythematosus (SLE) is a chronic, autoimmune, immune complex-mediated disease affecting mainly females at a young age. The disease etiology is still unknown, and different genetic and epigenetic factors related to disease onset and manifestations are being explored. The standard treatment regimen for SLE includes the long-term use of corticosteroids and non-specific immunosuppressive agents, often limited by co-morbidities or related side effects. However, recent advances in disease pathogenesis clarifying the role of inflammatory cytokines, chemokines, immune cells, and co-stimulation molecules have made a more practical, targeted approach possible, leading to personalized treatment strategies. This review summarizes current knowledge about SLE-targeted therapies in clinical practice.

Keywords: systemic lupus erythematosus; autoimmune; pathogenesis; cytokines; chemokines; cells; co-stimulation molecules; treatment; CAR T cell therapy

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1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune condition involving multiple organ systems and affecting predominantly women of childbearing age [1,2], with African Americans commonly affected [3]. As per the latest European Alliance of Associations for Rheumatology (EULAR) 2023 update [4], the current standard treatment of SLE includes nonsteroidal anti-inflammatory drugs (NSAIDs) for symptomatic relief and the antimalarial drug hydroxychloroquine (Plaquenil), which is recommended for all patients and corticosteroids (CS). Additional options are immunosuppressants and biologics that provide precise, targeted therapy, which opens doors for new treatment options [5,6]. However, the trend in terms of SLE management has turned progressively towards the research and development of novel targeted therapies, explicitly expanding their availability in the process [7–9]. Additionally, there is a current need for a holistic approach to SLE treatment that combines lifestyle modifications (e.g., smoking cessation, exercise) [10–12] with expanded therapeutic options, where new targeted therapies come in handy, providing wide-ranging opportunities to accomplish optimal disease outcomes. Since SLE is characterized by its heterogeneity [13], no single treatment plan can always apply to all patients. This issue renders the need for more individualized and novel targeted therapies that can address this concern precisely. For example, the tendency in recent years has been to aim for a

weaning off CS [14] and other immunosuppressive drugs for long-term usage in SLE [15,16]. Therefore, biologic agents are an excellent alternative to control the disease progression and reduce flares effectively [17], while having fewer adverse effects than immunosuppressants [18]. This brings hope to the currently difficult management of SLE when it comes to accomplishing the treat-to-target strategy [19,20], which ultimately assures adequate disease remission. Moreover, targeted therapies have shown promising results in handling one of SLE's most serious manifestations: lupus nephritis (LN) [21,22].

Furthermore, the efficacy of various SLE medicines has been observed to vary between ancestries, ethnicity, and genetic background, which may influence disease development and course and shape therapeutic responses. However, it is unclear if these differences are pharmacogenetic [23,24]. Moreover, a phenotypic and genomics approach is preferable in a multi-ethnic cohort to subtype SLE [25].

Still, there is a need for more precise and personalized therapy for SLE patients. This comprehensive review provides a concise overview of the latest advancements in SLE management, focusing on targeted therapies in clinical settings, including B-cell therapies, anti-cytokines, small molecules, co-stimulatory therapies, and CAR T cell therapies.

2. SLE Overview: Etiology and Pathogenesis as a Basis for Novel Tailored Therapy

SLE is a chronic, autoimmune, immune complex-mediated disease affecting mainly females at a young age. The etiology is still unknown, with genetic and epigenetic factors contributing to disease pathogenesis and clinical presentations [26]. The disease is characterized by the production of autoantibodies against nuclear antigens, immune complex depositions in various tissues, and subsequent complement activation leading to cell migration, tissue damage, and organ failure.

The exact cause of SLE remains unknown; however, various genetic, epigenetic, environmental, and hormonal factors are believed to contribute to its development [27]. Although genetic factors play a significant role, they are not solely responsible for SLE onset and need additional environmental triggers for the disease to manifest [28]. Generally speaking, many autoimmune diseases arise from the intricate interaction between genetic susceptibility and environmental risk factors. Genetic factors that contribute to the pathogenesis of SLE are being studied thoroughly, and new ones are being identified [29]. Additionally, hormonal factors may contribute to the development of SLE. Conditions characterized by elevated estrogen levels, such as the use of oral contraceptives, hormone replacement therapy in postmenopausal women, and endometriosis, are linked to an increased risk of SLE [30]. It is important to note that drugs such as procainamide or hydralazine can cause drug-induced lupus erythematosus [31].

The interplay between genetic susceptibility and environmental exposures can lead to epigenetic changes that dysregulate immune responses and contribute to the development and progression of SLE [32,33]. Many immunological factors concerning SLE pathogenesis, such as TNFa, IFN, IL-17, and other cytokines, have been investigated. Furthermore, meta-analyses show that gene polymorphism, such as that in the TNF-α gene, could be associated with SLE predisposition [34,35]. However, TNF-α is a proinflammatory cytokine that plays a role in the pathogenesis of various autoimmune disorders and is not limited to SLE. Similarly, interferon (INF) type I is central to SLE development and progression [36–39]. By activating dendritic and B-cells, type I INF facilitates immune dysregulation, which is a significant propelling element in the pathogenesis of SLE [40].

Furthermore, INF is also responsible for heightened inflammation and tissue damage in SLE as well as the amplification of the immune response by enhancing the expression of major histocompatibility complex (MHC) molecules on antigen-presenting cells and promoting the activation and differentiation of T cells, which further exacerbate the ongoing inflammation and tissue damage [40]. The deficiency in classical complement proteins (C1q, C4, C2) also leads to macrophages' inability to phagocytose immune complexes and apoptotic cell material, such as plasma and nuclear antigens. This failure results in dysregulated and intolerant lymphocytes targeting intracellular antigens, usually hidden.

This ultimately leads to the production of autoantibodies, such as antinuclear antibodies (ANAs) and anti-double-stranded DNA (anti-dsDNA) antibodies as well as anti-Smith, anti-Ro/SSA, and anti-La/SSB antibodies [41].

Lastly, type III hypersensitivity reactions are common in SLE, involving the formation of antibody–antigen complexes in the microvasculature. This leads to complement activation and inflammation, damaging various organs [42]. In contrast, type II hypersensitivity reactions involve IgG and IgM antibodies targeting antigens on cells, leading to different cytopenias, like anemia [43].

All advancements in understanding the pathogenesis of SLE have paved the way for developing novel targeted therapies designed to manage autoimmune responses effectively. In Figure 1, we present an overview of the factors related to SLE pathogenesis.

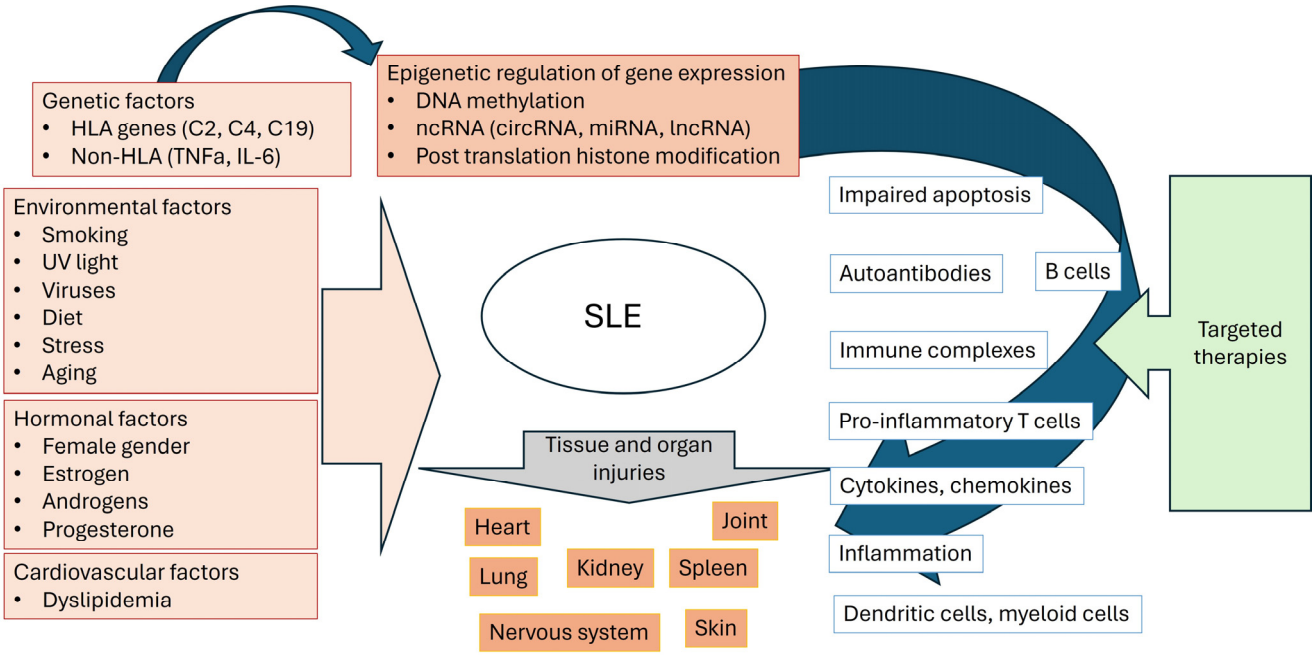

Figure 1. Factors for SLE development and pathogenesis, including immune mechanisms, targeted organs, and targeted therapies.

3. Treatment Options for SLE

Compared to other rheumatic disease treatments, SLE is still lagging in replacing traditional therapeutic approaches with novel venues. Traditional treatment agents include CS, antimalarials (hydroxychloroquine), and conventional immunomodulating/ immunosuppressive agents (azathioprine, methotrexate, cyclophosphamide, cyclosporine A, mycophenolate) [44]. Recently, the "treat-to-target" treatment strategy initially developed for rheumatoid arthritis (RA) management was conceptually extended and applied to SLE patient management [45]. Adhering to the latest EULAR and ACR recommendations [4] for the application of conventional disease-modifying drugs (csDMARDs), hydroxychloroquine could be used for all SLE patients at a target dosage regimen of 5 mg/kg body weight unless clear contraindication is present. However, this target regimen could be individualized upon considering the risk of flare or higher risk factors (i.e., kidney disease, preexisting macular or retinal disease, tamoxifen) predisposing patients to retinal toxicity. Due to its proven efficacy in reducing disease flares, safety, and low cost, hydroxychloroquine resembles the cornerstone of SLE therapy. It is eligible for long-term usage in combination with other therapeutic regimens [46,47].

Regarding CS usage, the latest recommendations set the maximal acceptable threshold to 5 mg/day prednisone equivalent for maintenance therapy in comparison to 7.5 mg/day in the 2019 recommendations. Furthermore, complete CS withdrawal should be considered

as the optimal target when possible, which conceptually reorientates CS usage for SLE as a "bridging therapy" tool [4].

A lack of therapeutic response to hydroxychloroquine as a single-line therapy or in combination with CS or the inability to reduce the dosage regimen below the maintenance dosage often determines a need to add an immunosuppressive agent as a second-line therapy for mild non-renal cases of SLE. In those cases, methotrexate, azathioprine, or mycophenolate can be added. Moderate or severe cases of non-renal SLE and LN, on the other hand, could require more complex treatment strategies involving the usage of cyclophosphamide (a low dose often combined with belimumab for LN or a high dose), a calcineurin inhibitor (often combined with mycophenolate), and target therapies, such as belimumab, anifrolumab (for non-renal SLE), and rituximab (for severe or refractory patients) [4].

However, conventional immunosuppressive agents have adverse effects and limitations, such as a broad spectrum of target organ injuries or disease relapses after the discontinuation of therapy. Since long-term disease remission should be achieved in therapeutic approaches that target the establishment of self-tolerance to SLE-associated autoantigens, many SLE patients seem to be trapped in a vicious cycle of disease exacerbation followed by immunosuppressive intervention. Thus, it was shown that long-standing disease remission could not be achieved using broad immunosuppressive agents alone [48]. Therefore, the need for novel SLE-tailored therapeutic strategies centered around fundamental SLE dysregulation mechanisms comes even more to the fore.

3.1. B Cell-Directed Therapy for SLE

B cell-directed therapy for SLE has been investigated in multiple studies, systematic reviews, and meta-analyses that have contributed to the understanding of the efficacy and safety of this form of treatment [49]. Representatives of B cell-directed therapy include rituximab, ocrelizumab, and ublituximab, monoclonal antibodies that target CD20 antigens on the surface of B cells [50], and belimumab, which targets B lymphocyte stimulator-BlyS.

Unfavorably, the LUNAR study (2012) found that rituximab therapy did not enhance clinical outcomes after one year in individuals with active proliferative LN who were also treated with mycophenolate mofetil and CS [51]. The study demonstrated that although rituximab reduced CD19 + B cells and anti-dsDNA antibody levels while increasing serum levels of complement factors (C3 and C4), renal response rates were comparable across the treatment and placebo groups (45.8% and 56.9%, respectively). Furthermore, patients receiving rituximab had a higher incidence of side events such as hypotension and neutropenia [51].

However, a metanalysis of Wu et al. (2020) that included two randomized controlled trials (RCTs) and 13 observational studies, with a total of 742 patients, demonstrated notably decreased peripheral CD19 + B cells and increased C3 and C4, resulting in a net change in disease activity score and confirming rituximab effectiveness and safety for SLE [52].

The results of the latter meta-analysis overlap with the outcomes from another systematic review conducted by Cobo-Ibáñez et al. 10 years ago, which demonstrated rituximab safety and effectiveness in treating non-renal SLE, particularly when it comes to disease activity, immunologic markers, and the sparing of CS. However, the authors concluded that rituximab could only be advised for organ-specific symptoms like thrombocytopenia and arthritis [53].

On the contrary, a systematic review by Weidenbusch et al. (2013) indicated that in SLE with LN patients who have not obtained remission from traditional therapy, rituximab is an effective way to induce remission [54]. On the other hand, Borba et al. demonstrated that despite its good safety profile, rituximab showed no superiority over a placebo in terms of efficacy in SLE [55].

Belimumab is currently the only B-cell-directed therapy for SLE that the FDA and EMA have approved. Belimumab is a monoclonal antibody that blocks B lymphocyte stimulator-BLyS, essential for activating B cell function [49]. BLISS-52 and BLISS-76 are

two phase III studies investigating belimumab's effectiveness (a biologic agent that targets B cells) in SLE. The results showed that the administration of belimumab, in addition to standard therapy, led to improvements in inflammatory indices and clinical symptoms of SLE in some subgroups of patients [49,56].

Another phase III trial focused on the long-term safety and efficacy of belimumab in SLE. The results showed improved inflammatory parameters and reduced SLE activity in patients receiving belimumab [57]. In their meta-analysis, Wei et al. (2016) estimated the efficacy and safety of therapy with belimumab compared with a placebo plus standard therapy in patients with SLE. The results suggested that treatment with belimumab plus standard therapy is more effective than a placebo plus standard therapy in SLE patients, representing major progress in the treatment of SLE. Regardless of the statistical analyses, further research is necessary to optimize treatment effects [58].

Similarly, in their systematic review and meta-analysis, Borba et al. (2014) evaluated the efficacy, safety, and tolerability of biologic drugs compared with a placebo for SLE. Belimumab exhibited a satisfactory profile regarding efficacy, safety, and tolerability. Biologic agents exhibited a good safety profile for SLE treatment, indicating that these agents are promising therapies and should be further investigated [55]. Regarding adverse reactions and loss of efficacy, despite the positive results of these studies and meta-analyses, B cell-directed therapy may be associated with various adverse reactions and loss of effectiveness. Adverse reactions related to the use of belimumab include nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, limb pain, depression, migraine, pharyngitis, cystitis, leukopenia, viral gastroenteritis, serious infections, depression-related events, suicidal ideation, fatal infections, and serious psychiatric events [59].

In conclusion, B cell-directed therapy aims to regulate or reduce B cell activity through various therapeutic strategies, such as monoclonal antibodies, selective inhibitors, and other drugs that target specific molecules or signaling pathways on B cells. Furthermore, this therapy controls unwanted immune responses associated with SLE and RA.

3.2. Co-Stimulatory Molecules for SLE

Co-stimulatory molecules are essential signaling molecules that activate the immune system and control the immune response. They play a crucial role in regulating the activity of T cells and other cellular elements of the immune system [60]. No medications are approved explicitly as co-stimulatory molecules for treating SLE yet. However, considering the pathogenesis of SLE, some of the most essential co-stimulatory molecules include the following. CD28 is a crucial molecule for T-cell activation. It binds to B7 molecules (CD80 and CD86) that are found on the surface of other cells, such as antigen-presenting cells (APCs) like macrophages or dendritic cells [61].

Similarly, CTLA-4 (cytologic T lymphocyte antigen 4) is an inhibitory receptor expressed on the surface of activated T cells. It competes with CD28 to bind to B7 molecules (CD80 and CD86), but with higher affinity, inhibiting T-cell activation [62]. Another molecule is ICOS, a co-stimulatory receptor that is expressed on activated T cells. It regulates the immune response by binding to ICOS-L (ICOS-Ligand), found on the surface of other cells, such as B cells and dendritic cells [63]. CD40 and CD40L are molecules expressed on the surface of B cells (CD40) and activated T cells (CD40L). They are involved in the stimulation and differentiation of B cells and the immune response [64].

For the therapy of SLE, various co-stimulatory molecules are being investigated as potential targets for new drugs. Since CD40 is a co-stimulatory molecule that plays a vital role in activating the immune system, studies suggest that the inhibition of the interaction between CD40 and its ligand (CD40L) may benefit the inflammatory characteristic of SLE [65].

Dapirolizumab pegol is composed of an anti-CD40 ligand Fab'antibody fragment connected to polyethylene glycol, included in phase IIb clinical trials that demonstrated clinical improvement, declined anti-DNA antibodies, and normalization of C3 and C4 [66].

Additionally, dapirolizumab pegol showed a good safety profile with a low risk of thromboembolic events [67]. Ramanujam et al. also rediscovered the role of the CD40-CD40L pathway in SLE and LN, emphasizing the blocking of this pathway to ameliorate systemic inflammation and nephritis [68,69]. Furthermore, the role of CD40-CD40L was confirmed in murine SLE models and cultures of cells in SLE patients [70,71].

Given the fact that B7 (B7-1 and B7-2) molecules interact with T cell receptors and play a vital role in regulating the immune response, modulating this interaction may be a potential strategy for treating SLE [72]. Similarly, a ligand for 4-1BB (CD137) is a co-stimulatory molecule expressed on activated T cells. Some studies have shown that blocking or stimulating 4-1BB may have anti-inflammatory or immunomodulatory effects that may be useful in controlling SLE [73].

3.3. Targeting Intracellular Signaling via JAK Inhibitors in SLE

The discovery of targeted small-molecule therapies, including Janus kinase (JAK) inhibitors, changed the therapy paradigm for some disorders. Through suppressing intracellular signaling (i.e., JAK protein–signal transducer and activator of transcription (STAT) transcription factors pathways), JAK inhibitors exert the potential for effectiveness in many autoimmune diseases, including RA, inflammatory bowel disease, spondylarthritis, alopecia areata, and some allergic diseases [74].

Through JAK-STAT, cytokines from the innate immune system communicate with adaptive immunological systems, such as autoreactive T cells, B cell activation, and autoantibody formation. These processes may be used as therapeutic targets for SLE [74,75]. Furthermore, convenient administration, reduced production costs, and non-immunogenicity benefit these targeted molecules [76,77].

In line with this, Nikolopoulos et Parodis focused on the clinical application of JAK inhibitors in SLE [78]. Data showed that in individuals with SLE, tofacitinib, a JAK1/3 inhibitor, decreased the type I interferon signature, improved vascular function, and lowered cholesterol levels [79]. Baricitinib, a JAK1/2 inhibitor, has been tested in one phase 2 trial, which showed notable improvements in lupus rashes and arthritis, and two phase 3 trials, which did not confirm these findings [80–82].

More extensive phase 3 trials will examine deucravacitinib, a selective tyrosine kinase 2 (TYK2) inhibitor, which produced higher response rates than a placebo in a phase 2 trial in SLE [83]. However, using JAK inhibitors necessitates carefully considering their multi-target effects, including sufficient screening and regular monitoring for infection, cardiovascular problems, thrombosis, and cancer [84–86].

A systematic review and meta-analysis on the efficacy and safety of JAK inhibitors in SLE and cutaneous lupus by Ma et al. highlighted that although JAK inhibitors were superior to a placebo in managing SLE and treating musculoskeletal and mucocutaneous involvement, they are not approved for SLE yet [87].

Therefore, why do we need JAK inhibitors in SLE? Richter et al. [88] answered this question by pointing out that none of these treatments has been approved for clinical practice despite encouraging outcomes from clinical trials. So far, using tofacitinib and baricitinib has shown the best outcomes. Owing to its intricate etiology, the treatment of SLE is evolving. Although JAK inhibitors are therapeutically helpful, how they relate to SLE is unclear. Although the safety and efficacy profiles indicate promising outcomes, more clinical trials are required. However, all the data released thus far are a foundation for upcoming research that should yield new and helpful insights into treating SLE patients [88].

3.4. Targeting Cytokines and Interferon and Kinoid Vaccines in SLE

Because cytokine production is different in SLE patients and may change during the disease [89], interferons and some inflammatory cytokines have been investigated for therapeutic purposes. A recent systematic review showed that more than 15 cytokine-targeting

molecules had been discovered for the targeted therapy of SLE in clinical practice [20]. Here, we will focus on the most promising targeted therapies currently in clinical development.

3.4.1. IL-2

Interleukin-2 (IL-2) and regulatory T cells (Tregs) are essential in promoting and maintaining immune tolerance. In patients with SLE, there are low levels of this interleukin, which leads to defects in Treg cells [90]. With low-dose IL-2 therapy, this deficiency can be reversed and restore immune tolerance [91–93]. In an open-label phase I/II trial with SLE patients, more than 80% showed a significant immune response and increased Treg cells [94]. Although this trial is in its initial phases, it has demonstrated that low dosages of IL-2 can improve Treg abnormalities linked to IL-2 deficiency in SLE patients. Furthermore, low-dose IL-2 therapy restores endogenous immunological tolerance mechanisms, thereby proposing a targeted biological treatment method that directly targets the pathophysiology of SLE [94].

The role of IL-2 has been evaluated in two RCTs with a good safety profile and clinical response [95,96]. He et al. demonstrated declined SLE Responder Index-4 in an IL-2-treated group vs. a placebo at week 12 ($p = 0.052$) and week 24 ($p = 0.027$). Furthermore, low-dose IL-2 treatment resulted in remission in 53.8% of patients with LN. No severe infections were recorded in the IL-2 group and two were recorded in the placebo group [95]. Similarly, Humrich et al. conducted a post-hoc hierarchical analysis of the primary and critical secondary endpoints in a per-protocol population, together with an exploratory analysis of many other secondary endpoints. The outcomes supported that low-dose IL-2 is advantageous in active SLE [96,97].

Placebo-controlled trials of low-dose IL-2 are Aldesleukin (NCT03312335), Efavaleukin Alfa (NCT03451422), LUPIL-2 trial with ILT-101 (NCT02955615), IL-2 with Telitacicept (NCT05339217), and CNTY-101 (NCT06255028) [98].

3.4.2. IL-6

Interleukin 6 (IL-6) is a cytokine with pleiotropic effects and has been found to be elevated in SLE patients [99–103]. PF-04236921, a human monoclonal IL-6 antibody, was investigated in SLE clinical trials but failed to demonstrate efficacy [104,105]. Another promising antibody, sirukumab, failed in the phase II trial [106]. Tocilizumab, a human monoclonal against the IL-6 receptor (IL-6R), was evaluated in an open-label phase I study [107]. The monoclonal antibodies MRA003US (NCT00046774) and CNTO 136 (NCT01702740) have no published results.

3.4.3. IL-17

Interleukin 17 (IL-17) is involved in the pathogenesis of rheumatic and musculoskeletal diseases. In SLE patients, increased Th17 cells and high levels of IL-17 in serum have been observed [108]. A human monoclonal antibody, secukinumab, was in a phase III clinical trial [109]. However, the study was terminated due to a futility analysis. There is one more trial in the database for IL-17, which is from 2021, but it has an unknown status (NCT05045417). The outcomes for SLE have been unfavorable so far; however, case reports have demonstrated the efficacy of secukinumab for LN refractory treatment, as reported by Costa et al. [110]. Nevertheless, other authors reported secukinumab-induced SLE in psoriatic arthritis [111] and ankylosing spondylitis [112].

3.4.4. IL-12/23 Axis

In patients with active SLE, there are increased serum levels of IL-23 compared to healthy individuals, which limits the in vitro production of IL-2 [93]. IL-12 is also involved in the pathophysiology of SLE [113]. Activation of the IL-23/IL-17A axis leads to an increased amount of Th17 cells, which ultimately contributes to the pathogenesis of LN [114,115]. In connection with these data, a monoclonal anti-IL-12/23 antibody, ustekinumab, targeting the p40 subunit shared by the cytokines IL-12 and IL-23, has been

reported [116]. This is an up-and-coming option for the terminated phase III trial, and safety and adverse effects are similar to those reported by other studies.

3.4.5. IL-10

Interleukin 10 (IL-10) has anti-inflammatory and proinflammatory effects, which are pathogenic in SLE [117]. A study shows that IL-10 serum levels are increased in SLE patients. The correlation with disease status is robust [118]. The anti-IL-10 antibody has completed a phase II trial (NCT02554019) and has results [119].

Hannon et al. included sixty-one RCTs involving 11,232 participants and reported 43 different interventions for cutaneous disease in SLE, including the trial mentioned above in their analysis. They concluded that evidence supports the commonly used treatment hydroxychloroquine and the combination of chloroquine and methotrexate. However, further data analyses and more trials designed to detect differences in the efficacy of anti-cytokines are needed [120].

3.4.6. Interferons

Interferon is a key cytokine in the pathogenesis of SLE, which is supported by numerous animal and human findings [121–124]. SLE patients have increased levels of type I IFN, and the genes are highly expressed in the peripheral blood [125–127]. Given the potential of IFNs to initiate or enhance immune responses leading to organ damage in lupus, many biologic therapies targeting IFNs are under investigation. Various strategies to develop interferon-targeted treatment have been tried over the years but have been largely unsuccessful. Subsequently, several molecules have been identified that target the IFN pathways and the IFNAR receptor, which signals intracellularly through JAK1/Tyk2 [128–130].

Anifrolumab (MEDI-546) is a monoclonal antibody against IFNAR1. After a successful phase, two open-label trials (MUSE) were approved for fast-track status by the FDA in 2021 [131–133]. Two other phase 3 studies were conducted in active SLE (TULIP-1 and TULIP-2) [134,135]. The first trial reported a negative primary endpoint (SRI-4) [134] and TULIP-2 reported positive results [135]. The discrepancies between the two trials are related to the selection of SRI-4 and a subgroup of lower disease activity SLE [136]. The use of anifrolumab in LN was investigated in the phase 2 TULIP-LN study [137]. A phase 3 trial (IRIS, NCT05138133) has started and is expected to end in 2027. It was shown that only phase 4 studies can accurately assess the safety of new SLE drugs.

Since anifrolumab was approved for moderate and severe SLE treatment, the post-hoc analysis confirmed its better efficacy in patients with a high type I IFN signature than in patients with a low type I IFN signature [138]. At the moment, anifrolumab is indicated for SLE without renal or CNS involvement.

Another anti-IFNα monoclonal antibody, sifalimumab, has been studied in a phase II trial in patients with moderate to severe SLE [133]. The most common complication reported was herpes zoster in patients receiving the high dose. The study reported positive results, although the effect was relatively modest. Rontalizumab is another human anti-IFNα antibody and was evaluated in a placebo-controlled phase II trial [139]. The severe side effects were relatively acceptable and classified as unrelated to the drug. The higher doses would be more effective, but the trials were stopped.

It was shown that IFNα kinoid, i.e., IFNα immunogen appropriately adjuvanted, produced short-lived neutralizing antibodies (Abs) but had no discernible adverse effects and no cellular immunological response to the cytokine in a murine model. Clinically, kinoid-vaccinated NZB/W mice showed reduced lupus manifestations, including proteinuria, histological renal lesions, and death triggered by IFNα adjuvant challenge [140].

A phase IIb, randomized, double-blind, placebo-controlled study was conducted for IFNα-kinoid (NCT02665364) in patients with active SLE [127,141]. IFN-K had a significant corticoid-sparing effect, but the evidence was limited and of moderate quality. Despite all the potential improvements in the understanding of the pathogenesis of SLE, the need for accurate treatment is still high. The development of new therapeutic agents in SLE

will allow for the discontinuation of CS and the achievement of remission or low-disease activity and remission.

3.5. CAR T Cell Therapy in SLE

A revolutionary new approach for SLE treatment is using genetically modified treatments with chimeric antigen receptor (CAR) T-cells designed to specifically target other cells or molecules with a main pathogenic role for disease onset and progression [142]. CARs are recombinant receptors coupled to autologous T cells to target a specific antigen. Targeting the CD19 antigen in SLE aims to induce a rapid and prolonged depletion of the circulating B cells in patients who failed to achieve clinical and/or serological remission on standard treatment protocols [143,144].

CAR Tcell therapy was first introduced by Schett et al. in a patient with refractory-to-standard treatment SLE, which achieved clinical drug-free remission for the whole follow-up period [145,146]. The authors recently reported a case series with 15 patients with refractory autoimmune connective tissue diseases (eight with SLE, three with idiopathic inflammatory Myopathies —IIM, and four with systemic sclerosis–SSc patients) who were treated with CAR T cells to achieve clinical and laboratory drug-free remission [147]. Research on CAR T cell therapy in refractory or relapsing autoimmune diseases, such as SLE, is progressing rapidly to improve treatment strategies and clinical outcomes in this kind of patient. Currently, several clinical trials are exploring the safety and efficacy of CAR T cell therapy in SLE or LN [148].

All of the novel targeted therapies in SLE discussed in this review are presented in Table 1.

Table 1. Novel targeted therapies for SLE patients.

Molecular Pathway and Corresponding Agent Tested in Clinical Trials in SLE			
Molecular Target	**Therapeutic Agent**	**Type**	**Results**
		B-cell inhibition	
BAFF/APRIL	Belimumab, Benlysta	Fully humanized IgG1 monoclonal antibody	Approved for active, antibody-positive, non-renal SLE
	Tabalumab	Fully human IgG4 monoclonal antibody	Failed to meet its primary endpoints
	Blisibimod	Fusion protein	Failed to meet its primary endpoints
	Atacicept	Fully human recombinant fusion protein	APRIL-SLE terminated; ADDRESSII had a better safety profile
CD20	Rituximab	Chimeric monoclonal antibody	LUNAR/EXPLORER-negative; accoring to EULAR it could be used aslast choice for severe refractory lupus
	Ocrelizumab	Fully humanized monoclonal antibody	Trials were terminated because of severe infections
	Obinutuzumab	Fully humanized monoclonal antibody	Phase III ongoing
CD22	Epratuzumab	Fully humanized monoclonal antibody	Phase III failed
CD19	XmAb5871	Monoclonal antibody	Under investigation
Proteasome inhibitors	Bortezomib	A modified dipeptidyl boronic acid	Terminated phase II trial because of adverse reactions

Table 1. *Cont.*

Molecular Pathway and Corresponding Agent Tested in Clinical Trials in SLE			
Molecular Target	**Therapeutic Agent**	**Type**	**Results**
Co-stimulation			
CD28/B7	Abatacept	A fusion protein (CTLA4-Ig)	Ineffective in phase II in nephritis and general SLE
CD40/CD154	Dapirolizumab	PEG-conjugated antiCD40L Fab fragment	Ongoing
Intracellular signaling			
Bruton's tyrosine kinase	Fenebrutinib	Small molecule, tyrosine kinase	Good safety profile, failed to meet its primary endpoint
Calcineurin inhibitor	Voclosporin	Calcineurin inhibitor	Approved by FDA for lupus nephritis
JAK1	Upadacitinib	Small molecule	Phase III trial in SLE
JAK1/2	Baricitinib	Small molecule	Phase III discontinued
JAK1/3	Tofacitinib	Small molecule	Under investigation
Tyk2 (JAK4)	Deucravacitinib	Small molecule	Under investigation
Cytokines			
Interferon-α	Sifalimumab	Fully human monoclonal antibody	No effect; discontinued
	Rontalizumab	Humanized monoclonal antibody	Well tolerated, but no additional trials planned
	Anifrolumab	Fully human monoclonal antibody	Approved for moderate and severe SLE and SLE nephritis
	IFN-K	Inactivated IFN-α coupled with protein	Failed to meet its primary endpoint
IL-2	Aldesleukin; AMG592	Cytokine	Under investigation
IL-12/23	Ustekinumab	Fully human monoclonal antibody	Suspended phase III over efficacy data
IL-6	Sirukumab	Fully human monoclonal antibody	Failed
IL-17	Secukinumab	Fully human monoclonal antibody	Phase III clinical trial
IL-10	Anti-IL-10 antibody	Fully human monoclonal antibody	Has completed a phase II trial (NCT02554019)
CAR T cell therapy	Chimeric–antigen receptors are recombinant receptors that are coupled to autologous T cells to target a specific antigen	-	In clinical trials for autoimmune diseases, incl. SLE

4. Conclusions

The evolving landscape of SLE management underscores the need for precise and targeted therapies. While CS and immunosuppressive agents have long been the mainstay, their limitations prompt exploration into novel approaches. Recent elucidations of SLE pathogenesis, particularly the genetics, epigenetics, and involvement of inflammatory mediators and immune dysregulation, have paved the way for personalized treatment modalities. By targeting specific molecular pathways, such as inflammatory cytokines and co-stimulation molecules, tailored interventions offer promising avenues for improved

outcomes. Based on their efficacy and safety in the clinical trials, we can speculate that the subsequent approved treatments will be JAK inhibitors and members of CAR T cell therapy.

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