Review

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Immunotherapeutic approaches for systemic lupus erythematosus: early overview and future potential

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Abstract: Systemic lupus erythematosus (SLE) is a complex autoimmune disease. Current SLE therapies include immunosuppressants, antimalarial drugs, non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids, but these treatments can cause substantial toxicities to organs and may not be effective for all patients. In recent years, significant progress has been made in the treatment of SLE using immunotherapy, including Benlysta and Saphnelo. These advances in immunotherapy hold promise for SLE patients, providing new therapeutic options that may offer better clinical benefit and effectiveness. Simultaneously, several new biological therapies focusing on cytokines, peptides, targeted antibodies, and cell-based approaches are under clinical evaluation and have shown immense potential for the treatment of SLE. However, the complexity of SLE immunopathogenesis and disease heterogeneity present significant challenges in the development of effective immunological therapies. This review aims to discuss past experiences and understanding of diverse immunological targeting therapies for SLE and highlight future perspectives for the development of novel immunological therapies.

Keywords: systemic lupus erythematosus; immunotherapy; innate and adaptive immunity

Introduction

Systemic lupus erythematosus (SLE) is a chronic, intricate autoimmune disorder marked by auto-antibody production and excessive inflammation, resulting in tissue damage. Its clinical severity varies, from mild to life-threatening, with diagnosis relying on detecting serum auto-antibodies against nucleus components and related proteins [1]. Despite advances in SLE treatment, including immunosuppressive agents, early diagnosis, and management over the last five decades, complications like inflammation, osteoporosis, cardiovascular issues, acute renal failure, and lupus nephritis persist and are on the rise. This underscores the demand for more potent therapies [2–4]. To attain full clinical effectiveness and address conventional therapy limitations, utilizing biological therapies through recombinant proteins and advanced molecular engineering holds promise for treating SLE and its complications. For example, Benlysta depletes B cells by impacting their survival factors, reducing the production of autoantibodies, either alone or in conjunction with traditional treatments [5]. Saphnelo blocks type I interferon (IFN-I) receptor to mitigate inflammatory responses [6]. Furthermore, recent extensive research into SLE's intricate pathogenesis, including experimental models, gene screening, and data analysis, has pinpointed various crucial biological molecules involved in SLE development. These molecules are promising candidates for therapeutic targeting. In this review, we will not only discuss the benefits and limitations of immunological therapeutics used to treat SLE in the past, but also summarize the emerging and potential new biological medicines that are likely to offer improved therapeutic options for SLE.

SLE immunopathogenesis

Innate immunity in SLE

The innate immune system, involving cells such as neutrophils, macrophages/monocytes, and dendritic cells (DCs), serves as the primary defense against pathogens and plays a crucial role in SLE's development and pathogenesis (Figure 1). In SLE patients, impaired neutrophil/macrophage-driven

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clearance leads to lingering cell debris and an inability to remove fragments from necrotic and apoptotic cells. These fragments may potentially stimulate immune cells to produce auto-antibodies [7]. Abnormal macrophage activation triggers the release of multiple pro-inflammatory cytokines, activating adaptive immune cells to produce antibodies and a high level of cytokines. Additionally, an imbalance in M1/M2 macrophage polarization is observed in SLE. M1-polarized macrophages, with a pro-inflammatory response, become more dominant, characterized by increased CD86, signal transducer and activator of transcription (STAT) 1, and suppressor of cytokine signaling (SOCS) 3 expression. Conversely, the CD163-positive M2 macrophages, known for their anti-inflammatory function and tissue healing, are notably reduced. This M1/M2 macrophage imbalance disrupts immune homeostasis and tolerance in SLE [8].

The role of DCs in SLE

DCs participate in both innate and adaptive immunity. Blood DCs encompass plasmacytoid DCs (pDCs) and myeloid DCs (mDCs). pDCs, primarily expressing TLR 7 and 9, are significant sources of increased interferon-α (IFN-α) during the early phase of SLE. Their activation is triggered by engagement of toll-like receptors (TLRs) with self-RNA/DNA fragments and proteins, leading to a myeloid differentiation primary response 88 (MyD88) dependent signaling pathway. This pathway involves recruitment of tumor necrosis factor (TNF) receptor-associated factor (TRAF) 6, interleukin-1 receptor-associated kinase (IRAK) 4, and Bruton's tyrosine kinase (BTK) to induce interferon regulatory factor (IRF) 7 phosphorylation and IFN-α response [9]. In SLE patients, peripheral pDCs are reduced and have an increased capacity to induce T cell activation and proliferation, whereas most pDCs are highly identified and accumulated in skin lesions and renal glomerulus of SLE patients through pDCs migration from circulating to the injured site [10]. Eliminating pDCs in lupus-prone mice markedly reduces spleen and lymph node pathology, leading to suppressed T and B cell activation, lowered levels of various autoantibodies, and disrupted transcription of IFN-I-associated genes [11]. A recent study shows elevated $CD40^{+}$ $CD86^{+}$ mDCs in SLE patients' peripheral blood, along with increased high mobility group box 1 (HMGB-1) and mammalian target of rapamycin (mTOR) levels, indicating disease activity [12]. HMGB-1 triggers inflammation and is associated with autoantibody production, immune complex formation, and tissue damage in SLE through the HMGB-1/receptor for advanced glycation end-products (RAGE) signaling pathway [13].

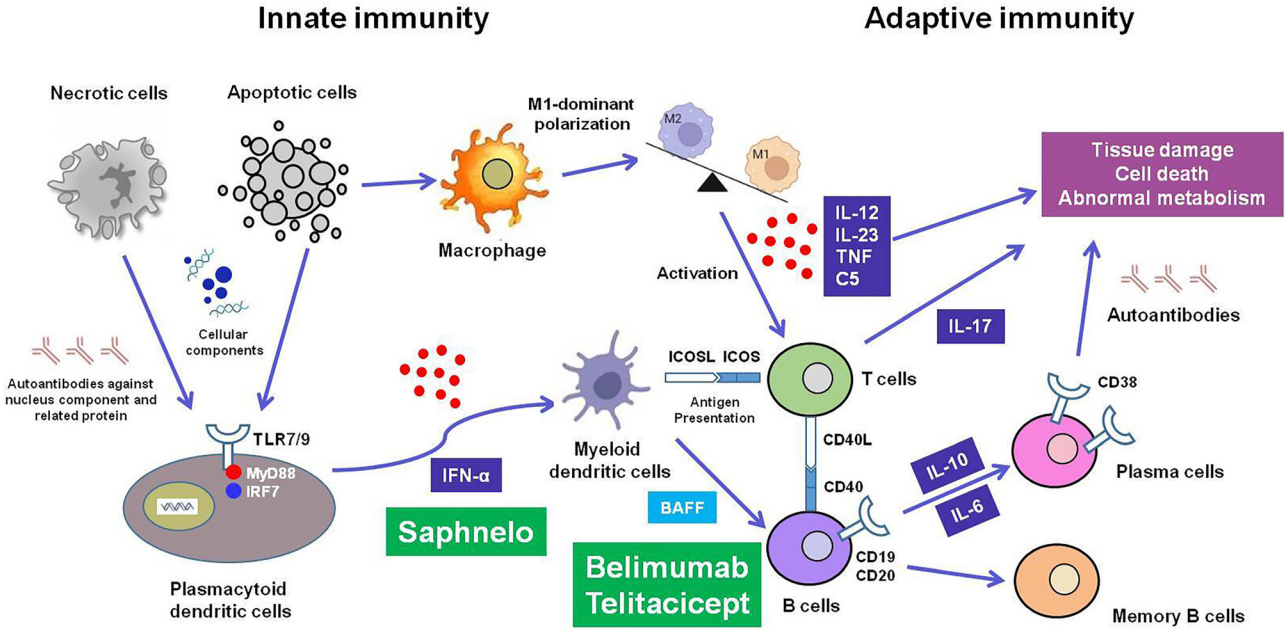

Figure 1: The role of innate and adaptive immunity in systemic lupus erythematosus (SLE) immunopathogenesis. BAFF, B cell-activation factor; ICOS, inducible T cell costimulator; ICOSL, inducible T cell costimulator ligand; IFN, interferon; IL, interleukin; IRF, interferon regulatory factor; MyD, myeloid differentiation primary response; TLR, toll-like receptor; TNF, tumor necrosis factor; C, complement.

Adaptive immunity in SLE

The role of T cells in SLE

Various aberrant signaling and metabolism in T cells contribute to the immunological pathogenesis of SLE. Mitochondria dysfunction-driven oxidative stress might be a cause for T cell-mediated pathogenesis of SLE. Mitochondrial hyperpolarization caused by chronic autoreactive T cells in SLE patients promotes reactive oxygen species (ROS) and high consumption of glutathione and cysteine deemed as antioxidant molecules [14]. Elevated ROS levels suppress DNA methyltransferase 1 (DNMT1) activity, resulting in gene hypomethylation and heightened expression of SLE-associated genes, such as CD70 and CD11b [15]. Oxidative stress is known to facilitate mTOR signaling, which plays a crucial role in mediating T cell activation, differentiation, and homeostasis. Activated mTOR drives the differentiation of naïve $CD4^+$ T cells towards type 1 T helper (Th1) and Th17 cell subpopulations, while also suppressing the differentiation of regulatory T cells (Tregs), essential for immune tolerance maintenance [16]. As previously mentioned, heightened ROS-induced DNMT1 inhibition hampers forkhead box P3 (FOXP3) transcription, thus impeding the differentiation of $CD4^+CD25^+$ Treg cells. Furthermore, serum interleukin-6 (IL-6) levels are significantly elevated in both lupus-prone mice and patients compared to healthy controls and have a positive correlation with disease activity scores [17].

The role of B cells in SLE

SLE is marked by heightened B cell activity and the breakdown of B cell tolerance, leading to autoantibody production and intensified inflammation. B-cell activating factor (BAFF) plays a crucial role in B cell survival, the maturation of bone marrow-derived transitional B cells, and the development of autoreactive B cells. In SLE patients, elevated circulating BAFF levels are confirmed and strongly associated with anti-dsDNA antibody levels and disease activity [18]. Research has identified abnormal B cell subtypes in SLE patients, including higher levels of $CD38^+CD27^+CD138^+$ plasma cells, $CD27^+IgD^-$ memory B cells, and $CD86^+CD95^+$ activated B cells. Conversely, SLE patients exhibit reduced $CD19^+/CD20^+$ naïve B cells, marginal zone B cells, follicular B cells, and IL-10-producing Breg cells [19–21].

CD40, a receptor presented on B cells, plays a crucial role in immune response by facilitating the interaction with T cells. Upon T cell activation, CD40L can bind to B cells via CD40, leading to isotype switching of IgG and contributing to the development of SLE. Studies have shown that CD40L is upregulated in SLE patients and is involved in the pathogenesis of the disease [22, 23]. In NZB/W lupus mice, treatment with anti-CD40L monoclonal antibody effectively delays disease onset, reduces urinary protein levels, and enhances the survival rate of mice. Therefore, targeting CD40 may offer a promising therapeutic approach for SLE [24].

Dysregulated CD38 expression profiles in peripheral immune cell subsets may potentially serve as detective biomarkers for SLE diagnosis. In patients with SLE, there is a notable increase in CD38 expression in multiple immune cell types, including pDCs, monocytes, marginal zone-like B cells, and memory T cells [25]. Moreover, an initial study has shown that elevated anti-CD38 IgG autoantibodies are often detected in clinically-defined quiescent patients and might offer some protective effects for individuals with specific clinical symptoms [26]. Hence, inhibiting the CD38 molecule to target plasma cells could be a promising therapeutic approach for SLE.

The role of cytokines in SLE

The IL-6/IL-10 signaling pathways have been shown to promote the differentiation of B cells into antibody-secreting plasma cells [27, 28]. Accumulating data have indicated that a reduction in IL-2 production is related to the imbalance in Treg/Th17 differentiation. Furthermore, abnormally increased expression of protein phosphatase 2A (PP2A) has been implicated in the reduction of IL-2 and promotes the production of IL-17 that is thought to be embroiled in pathogenesis of SLE [29]. IL-12, a pro-inflammatory cytokine, initiates and sustains Th1 responses via interferon-γ (IFN-γ) induction. It also promotes T-follicular helper (Tfh) cell development, contributing to SLE progression through STAT 1 and 4 activation [30]. Elevated serum IL-23 in SLE patients can stimulate IL-17 production. Research has shown that T cells from mice lacking IL-23 expression produce higher levels of IL-2 and lower levels of IL-17 [31].

Approved immunotherapy

Belimumab is a fully humanized monoclonal antibody (mAb) that specifically targets the soluble B lymphocyte stimulator (BLyS), also known as BAFF [32, 33]. FDA approval encompasses SLE and lupus nephritis (LN) treatment in adults and children as shown in Table 1 [34]. BLISS-52 phase III trial demonstrated notable SLE responder index (SRI) response rate improvement in active, autoantibody-positive SLE patients given 1 mg belimumab vs. placebo at week

52 (43.2 % vs. 33.5 %; p=0.017) [35]. PLUTO phase II trial enrolled 93 childhood-onset SLE (cSLE) subjects receiving monthly intravenous 10 mg belimumab (n=53) or placebo (n=40). Belimumab-treated patients achieved numerically higher SRI-4 response at Week 52 compared to placebo (52.8 % vs. 43.6 %). Serious adverse events were less frequent in belimumab-treated patients (17.0 % vs. 35.0 %) [36]. A phase III multinational and multicenter trial highlighted a significant improvement in clinically complete renal response with belimumab-treated adult LN patients at Week 104 (30.0 % vs. 20.0 %, p=0.02) relative to placebo [37]. Overall, belimumab's approval signifies a major advancement in targeted SLE therapies after 50 years, fostering potential for similar medication development, and expanding therapeutic options for lupus patients.

Saphnelo is a fully humanized mAb approved in 2021 for adult SLE treatment. It targets IFN-I receptor subunit 1, inhibiting STAT 1 and STAT 2 phosphorylation. Positive data from MUSE phase II and TULIP 1/2 phase III trials support this approval. In MUSE phase IIb, anifrolumab (300 mg or 1,000 mg) enhanced SRI-4 achievement at Week 24 compared to placebo [34.3 % (300 mg, p=0.014); 28.8 % (1,000 mg, p=0.063); 17.6 % placebo]. Sustained anifrolumab therapy further improved patients at Week 52 [38]. TULIP-1 showed reduced oral corticosteroid use, improved cutaneous lupus erythematosus disease, and British Isles Lupus Assessment Group-based composite lupus assessment in anifrolumab-treated patients [39]. TULIP 2 enrolled 362 subjects, with 47.8 % anifrolumab-treated patients exhibiting British Isles lupus assessment group-based composite lupus assessment (BICLA) responses compared to 31.5 % placebo. Highly interferon gene expressed patients showed 47.8 % BICLA response with anifrolumab and 30.7 % placebo. Low-interferon gene patients had 46.7 % (anifrolumab) and 35.5 % (placebo) BICLA responses. Anifrolumab reduced oral glucocorticoid dose, skin disease severity, and adverse events frequency [40]. Saphnelo's approval emphasizes targeting highly-expressed IFN-I levels in SLE, reflecting increased understanding of its complex pathogenesis.

Telitacicept is a recombinant fusion protein that combines the ligand-binding domain of transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) receptor with the Fc component of human IgG. Its pharmacological effect involves blocking the activity of two critical molecules: BLyS and a proliferation-inducing ligand (APRIL), which impact the development and survival of plasma cells and mature B cells. Telitacicept receives conditional marketing approval for adult SLE treatment in China in early 2021 and is anticipated to address various autoimmune disorders, including neuromyelitis optica, rheumatoid arthritis (RA), IgA nephropathy, and multiple sclerosis (MS) [41]. In a phase III confirmatory study, the data demonstrate that SRI-4 response was significantly higher in telitacicept-treated patients compared with placebo group (82.6 % vs. 38.1 %, p < 0.001). After re-analysis of data using multiple imputation for missing data, the clinical improvement in SRI-4 response in telitacicept-treated patients was still notably higher than those placebo patients (67.1 % vs. 32.7 %) [42]. A similarly-designed phase III trial to evaluate telitacicept efficacy against placebo in SLE patients is underway in US (NCT05306574). In addition, RemeGen is currently launching multiple clinical trial plans for the treatment of myasthenia gravis (MG), LN, IgA nephropathy, children SLE, and Sjogren's syndrome (SS) [43]. The approval of telitacicept in China marks another significant milestone advancement in the development of innovative therapies for SLE patients who have not responded well to other treatments.

Antibody-based immunotherapy

B cell-targeted therapy

Obexelimab is a humanized Fc-engineered monoclonal antibody (mAb) targeting CD19. It also binds to the inhibitory Fcγ receptor IIb (FcγRIIb) present on B cells, resulting in decreased B cell activity [44]. Currently, obexelimab has been evaluated in multiple clinical trials such as IgG4-related disease, rheumatoid arthritis, and SLE. In a phase II clinical trial with 104 patients, the results demonstrated that maintenance of improvement evaluated at Day 225 accounted for 42.0 % of obexelimab-treated patient and 28.6 % of placebo group, respectively (p=0.18). Of note, the patients treated with obexelimab had a significant longer time to loss-of-improvement than patients in the placebo group (p=0.025) [45]. Despite unmet primary endpoint, time to flare endpoint, well-tolerated property, and low infection rate have supported obexelimab further evaluation for SLE treatment. To identify the responders to obexelimab therapy, gene expression sequencing in immune-related pathways was performed using patient blood samples. Sensitivity to obexelimab was linked to heightened B cell and plasma cell pathway modules, indicating robust pharmacodynamic effects. Conversely, non-sensitive individuals exhibited increased expression of complement-mediated inflammation modules [46]. These hints imply the possibilities to establish precise therapy according genetic susceptibility profiles of different patients.

Rituximab (RTX) is a chimeric mAb that selectively targets $CD20^+$ B cells for treatment of specific hematologic malignancies through cell-mediated and antibody-mediated

cytotoxicity to deplete $CD20^+$ B cells. Since 2002, a series of early clinical trials to evaluate the outcome of RTX used in a small size of SLE patients had been conducted, showing promising potential for SLE treatment [47]. However, the results from an EXPLORER phase II/III trial to evaluate efficacy and safety of RTX in moderately-to-severely active SLE have shown that no significant difference is observed at Week 52 in major or partial clinical responses between the RTX group and placebo group. Some of patients have experienced incomplete B cell depletion that might influence the ultimate clinical outcomes. Oddly, the effectiveness measured by the primary and secondary end points was unchanged after exclusion of those patients [48]. The LUNAR trial demonstrated the overall renal responses had been demonstrated similarly in both RTX group and placebo group, although RTX caused significant reduction in anti-dsDNA and complement levels. Moreover, RTX combined with mycophenolate mofetil (MMF) and corticosteroids therapy failed to bring any significant clinical benefits [49]. Likewise, RTX plus cyclophosphamide therapy did not provide additional clinical improvement and effectiveness after 48 weeks of treatment relative to RTX monotherapy [50]. Notably, recent data from a phase II clinical trial have unveiled that belimumab therapy significantly promotes the reduction of serum IgG anti-dsDNA antibody levels and severe flare risk in SLE participants who are prior to RTX treatment and refractory to conventional treatment [51]. Given that optimistic data obtained from combinational therapy, a multicenter phase III clinical trial is ongoing to further investigate clinical efficacy of this novel approach in severe SLE [52].

Obinutuzumab is a humanized and glycoengineered type II anti-CD20 mAb indicated for chronic lymphocytic leukemia (CLL) combined with chlorambucil therapy and for follicular lymphoma (FL) in combination with bendamustine [53]. Obinituzumab is designed to break limitation and resistance induced by RTX based on clinical data and analyses [54]. Clinical study intended to evaluate obinutuzumab response in RTX secondary non-responding SLE patients had shown obinutuzumab treatment significantly led to reduction in disease activity score, with numerical or significant change in complement 3 (C3) and anti-dsDNA antibody levels post 6-month therapy. Notably, 6 out of 9 patients had complete peripheral B cell depletion. At 6 months, 5 of 8 patients reduced their dosage [55]. The ALLEGORY phase III study to evaluate the efficacy and safety of obinutuzumab in SLE patients is ongoing (NCT04963296). These results have proposed a novel therapeutic approach to treat SLE patients who failed to have clinical efficacy after secondary RTX therapy by obinutuzumab infusion.

Ofatumumab is a fully humanized CD20-directed cytolytic mAb. It was approved for the treatment of CLL in early 2009 and relapsing forms of MS in 2020. In a clinical trial, 16 patients with severe RTX-associated infusion reactions received ofatumumab infusion, 14 of whom were well tolerated and were achieved in B cell depletion and improvement in serological markers of disease activity [56]. Additionally, the clinical beneficial effects including reduced albuminuria level were observed in refractory LN patients who had RTX infusion reaction after treatment with ofatumumab at a dose of 700 mg two weeks apart [57]. More importantly, successful use of ofatumumab in juvenile SLE patients had been reported, suggesting that ofatumumab might be a treatment approach for SLE as an alternative to RTX [58, 59].

CD40-CD40L interaction-targeted therapy

Dapirolizumab pegol (DZP) is a potential SLE treatment, consisting of an anti-CD40 ligand Fab'antibody fragment linked to polyethylene glycol (PEG). It works by binding to and inhibiting CD40, a pivotal player in immune cell activation, ultimately reducing inflammation and ameliorating SLE symptoms [60]. In a phase IIb clinical trial, the results demonstrated that DZP treatment was effective in improving clinical measures of disease activity, reducing levels of anti-dsDNA, and normalizing C3 and C4 levels compared to the placebo group at Week 24. However, the highest dosage group of DZP (45 mg/kg) exhibited a slightly higher incidence of severe treatment emergent adverse events (TEAEs) than the other groups [61]. It is crucial to take into account the possible risk of thromboembolic events related to the administration of CD40L-targeting drugs [62]. Considering this fact, DZP showed a favorable safety profile, being generally well-tolerated, and having a lower risk of thromboembolic events than other anti-CD40L mAb [63]. DZP is currently in phase III clinical trials for SLE (NCT04976322).

CD38-targeted therapy

Daratumumab, a humanized anti-CD38 mAb initially approved for multiple myeloma, is under exploration for SLE and other indications. It functions by binding to CD38, triggering cytotoxic effects via complement-dependent cytotoxicity (CDC), antibody-dependent phagocytosis (ADP), antibody-dependent cellular cytotoxicity (ADCC), apoptosis, and immune regulation. In a clinical trial, two severe SLE patients treated weekly with daratumumab exhibited persistent clinical improvement, reduced systemic inflammation,

and a significant decrease in autoantibodies within four weeks, lasting for several months. Single-cell sequencing techniques verified daratumumab's beneficial impact on activated T lymphocytes [64]. These results are encouraging for larger clinical trials in the future.

Cytokines-targeted therapy

Ustekinumab is a fully humanized mAb that is used to treat autoimmune diseases such as psoriasis, psoriatic arthritis, and Crohn's disease through blocking the activity of IL-12 and IL-23 [65]. A phase III LOTUS trial, which was designed to investigate the efficacy and safety of ustekinumab in treating 516 patients with active SLE, was terminated due to insufficient clinical effectiveness, without any safety concerns [66].

Rezpegaldesleukin is a polyethylene glycol (PEG) conjugated fusion protein that is designed to target IL-2 receptor for treatment of autoimmune and inflammatory disorders including SLE and ulcerative colitis through increased level of Tregs to restore immune system balance. Recent study has reported that rezpegaldesleukin displays a reduced affinity to interleukin 2 receptor alpha (IL-2Rα), interleukin 2 receptor beta (IL-2Rβ), and interleukin 2 receptor alpha and beta (IL-2Rαβ) *in vitro*. In SLE-prone mice (MRL/MpJ-*Fas*^{lpr}), treatment with rezpegaldesleukin for 12 weeks improved disease development and progression through reduction of SLE serological biomarkers, declined urine protein concentration, and mitigation of kidney damage [67]. In a phase I study, treatment with rezpegaldesleukin twice a week was shown to induce a durable and significant increase in number of Tregs without notable alteration of peripheral T cells in participants [68]. These encouraging findings warrant further investigation into clinical efficacy of rezpegaldesleukin in adult patients with SLE (NCT04433585).

Traditional Chinese medicine in SLE

Rehmannia six formula

This treatment comprises six medicinal herbs: Prepared Rehmannia Root, Chinese Yam Rhizome, Asiatic Cornelian Cherry Fruit, Tree Peony Bark, Hoelen Mushroom, and Water Plantain Rhizome. Clinical trials combining Rehmannia Six Formula therapy with prednisone and cyclophosphamide showed significant improvements in 24-h proteinuria, erythrocyte sedimentation rate, C3 levels, and plasma albumin in lupus nephritis patients. Furthermore, it led to lower disease recurrence rates and fewer adverse effects compared to the control group [69, 70].

Artemisinins

Artemisinin, derived from *Artemisia annua*, is known for its strong antimalarial effects. Its promising attributes, including anti-inflammatory, immunomodulatory, and antioxidant properties, have sparked interest in its potential application for treating SLE. A clinical trial showed that combining Artesunate tablet, Lingdan tablet, and prednisone effectively reduced disease activity and improved symptoms like fever, joint pain, erythema, rashes, and hair loss.

Additionally, Artesunate combination therapy resulted in significant reductions in 24-h urinary protein and balance immune function [71].

Zhuang and Yao medicine

Zhuang and Yao medicine, as the essential branch of traditional Chinese medicine, have substantiated its efficacy in both preclinical investigations and clinical trials. The combination of Zhuang medicine cupping and pricking blood therapy has shown a significant improvement in the clinical symptoms of patients with arthralgia diseases. Moreover, Zhuang medicine thread Moxibustion has been observed to notably decrease the serum levels of tumor necrosis factor-α (TNF-α) and IL-1β [72–75].

Zhuang and Yao Medicine, rooted in China's Guangxi region, employs specific natural ingredients and techniques to restore bodily balance and promote healing. This involves customized treatments like herbal preparations, massages, and cupping, aimed at harmonizing qi and blood. The research patent demonstrates that the Yao herbal formulation notably diminishes the levels of IL-1β and TNF-α, along with reducing the severity of joint lesions in the rat model of RA (CN110638913A). Given this approach and philosophy, combining Zhuang and Yao Medicine with other therapies could hold promise as a clinical approach for treating SLE.

Emerging biological therapy

KP-104, as depicted in Table 2, is complement-based therapy targeted for immune-mediated disorders. As a first-in-class bifunctional biologic, KP-104 is designed to selectively and synergistically block upstream alternative pathway (Factor H) and downstream terminal pathway (C5), providing a powerful therapeutic tool in complement-mediated disease [76]. Preclinical study supported KP-104 beneficial pharmacological profiles for both intravenous and subcutaneous route. According to news provided by Kira Pharmaceuticals, KP-104 therapy is recently granted orphan drug

designation by FDA for treatment of paroxysmal nocturnal hemoglobinuria (PNH). A completed phase I first-in-human (FIH) study had shown the prominent clinical proof-of-mechanism (POM). Beside PNH indication, a non-randomized phase II study is recruiting participants with SLE associated with thrombotic microangiopathy (SLE-TM) in US, China, and Australia to investigate efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of KP-104 (NCT05504187).

Daxdilimab is a fully humanized mAb against immunoglobulin-like transcript (ILT) 7 expressed on the surface of pDCs, leading to cytotoxic effect of pDCs dependent on recruitment of the effector cells [77]. pDCs were the prominent immune cell type that were highly associated with production of IFN-I, which was a crucial driver in SLE [78]. Preclinical study had shown that daxdilimab-induced pDC depletion significantly reduced the IFN-I levels. Daxdilimab, therefore, is primarily expected to treat IFN-I-mediated autoimmune diseases. Early clinical data had provided the evidence that daxdilimab treatment reduced locally dermal pDCs and IFN-I levels, thereby inducing a durable improvement in disease activity with well-tolerated feature. Currently, a RECAST phase II study is underway to evaluate potentially therapeutic effect and safety of daxdilimab in treatment of moderate-to-severe discoid lupus erythematosus (DLE) (NCT05591222).

Litifilimab is a humanized IgG1 mAb targeting blood dendritic cell antigen 2 (BDCA2) receptor predominantly expressed on pDCs. It is being investigated the therapeutic potential in treatment of cutaneous lupus erythematosus (CLE) and SLE. In a phase II clinical trial with 132 patients with histologically confirmed CLE, treatment with litifilimab at Week 16 induced the considerable reduced skin disease activity score compared with placebo group, with rare antibody-treated adverse cases during the course of trial [79]. The results from another phase II study enrolled 334 patients with SLE, arthritis, and active skin disease who received different doses of litifilimab or placebo had demonstrated significant decrease in number of swollen and tender joints in litifilimab-treated group (19.0 ± 8.4) as placebo group (21.6 ± 8.5) over 6 months, although adverse events are occasionally observed in litifilimab-treated receipts, two cases of who had herpes zoster and one case in those patient experienced herpes keratitis [80]. With these positive data, there are two concurrent phase III clinical trials: TOPAZ-1 (NCT04895241) and TOPAZ-2 (NCT04961567), evaluating the efficacy and safety of litifilimab therapy about a period of year in active SLE patients against placebo treatment.

Itolizumab is a humanized IgG1 mAb against CD6 molecule as a co-stimulatory receptor mostly expressed in T cells and a subset of B cells. CD6 and its ligand, activated leukocyte cell adhesion molecule (ALCAM), have been demonstrated to contribute to T cell activation, trafficking, Th1/Th17 differentiation, as well as pathogenesis of SLE and LN disease [81]. In an EQUALISE phase Ib dose-escalation study, was divided by two parts: Itolizumab displayed well-tolerated in the receipts dosed from 0.4 mg/kg to 2.4 mg/kg. A half proportion of patients receiving 3.2 mg/kg were discontinued to further therapy after the first dose owing to the reduced tolerability. No serious adverse events (SAEs) were reported. The complete or partial response was achieved in 83 % of participants and over 80 % reduction in the ratio of urine protein and creatinine was observed in 67 % of subjects by 28 weeks. No treatment-related serious adverse events occurred [82]. The safety data combined with pharmacokinetics, pharmacodynamics, and clinical activity support further investigation in SLE patients.

Rigerimod, as a novel peptide-based treatment for SLE, is a synthetic 21-mer linear peptide derived from small nuclear ribonucleoprotein U1-70K [83]. Treatment with rigerimod caused inhibition of T cell activation, reduced expression of major histocompatibility complex class II (MHC II) in antigen-presenting cells (APCs), and decrease in proteinuria and anti-dsDNA antibody in lupus-prone mouse model [84, 85]. In a phase IIb clinical trial, rigerimod therapy significantly lessened disease activity and was efficacious and generally well tolerated with generally mild injection-site erythema [86]. Even though rigerimod showed no treatment-related serious adverse events and superior clinical response and remission, treatment with rigerimod (200 mg) every 4 weeks for 48 weeks concomitant with standard therapy did not demonstrate any improvement in disease activity of SLE in comparison with standard care alone in a phase III trial (NCT02504645). Notwithstanding these disappointing data, ImmuPharma is continuing to support rigerimod clinical program for the treatment of SLE by a higher dosing exploration under FDA guideline and recommendation.

Potential bispecific antibody therapy

Rozibafusp alfa is a first-in-class bispecific antibody-peptide conjugate that dually inhibits BAFF and inducible costimulator ligand (ICOSL). Preclinical study reported that treatment with rozibafusp alfa yielded significantly beneficial effectiveness in several mouse models with arthritis and lupus by dual inhibition of BAFF and ICOSL [87]. The data from a phase Ib study had shown that rozibafusp alfa therapy with multiple ascending doses in patients with active RA

were well tolerated, with 20 % of patients detecting anti-drug antibodies. Numerical improvement in disease activity was observed with rozibafusp alfa therapy relative to placebo [88]. A phase II trial for evaluation of efficacy and safety of rozibafusp alfa in participants with active SLE is ongoing (NCT04058028).

Tibulizumab is a subcutaneously administered dual-antagonist bispecific antibody that simultaneously targets BAFF and IL-17 for the treatment of autoimmune disease such as SS and RA [89]. The potential pathogenesis of SS might be implicated with abnormal T cell activation to damage epithelial cells and gland, excessive production of proinflammatory cytokines, and autoantibodies secreted by self-reactive B cells [90]. Preclinical study reported that tibulizumab effectively neutralized human BAFF and IL-17 activities and reduced B cells in a dose-dependent manner [89]. Currently, two phase I clinical studies to evaluate its efficacy and safety in treatment of SS and RA have completed. No further result and clue were reported.

PRV-3279 is novel biological therapeutic bispecific antibody against human CD32B and CD79B molecules on B cells for treatment of SLE and other autoimmune disorders. CD32B, also known as FcγRIIb, plays a key role in suppression of aberrant B cell activation, while CD79B is a subunit of B cell receptor associated with B cell activation. The potential pharmacological treatment of PRV-3279 is thought to activate CD32B inhibitory effect and spontaneously inhibit CD79B-mediated B cell activation [91]. Current available data have demonstrated that PRV-3279 was well-tolerated and reduced immune response by inhibitory pathway in a phase Ia single ascending dose study in healthy volunteers (NCT03955666). The PREVAIL-2 study to assess the safety and potential efficacy of PRV-3279 in flare prevention in SLE patients with active disease after amelioration induced by corticosteroid treatment is ongoing (NCT05087628).

Cell therapy

KYV-101 is a novel autologous fully human anti-CD19 CAR T therapy for B cell-induced autoimmune diseases, such as LN, systemic sclerosis, and inflammatory myopathies. KYV-101 is intended for reduction of inflammatory cytokine and autoantibody levels driven by B cells, providing a long-lasting and stable protective effect to destroy B cells. Recently, the FDA has granted permission for the first KYV-101 therapy candidate to begin clinical testing in lupus nephritis patients in early 2023 based on their undisclosed results in a phase I/II study to evaluate the efficacy and safety of KYV-101 therapy in 20 patients with B cell lymphoma [92, 93].

Mesenchymal stem cell (MSC) and MSCs-secreted exosome therapy has garnered significant attention and has been extensively investigated for the treatment of refractory autoimmune diseases in recent years due to their potential immunomodulatory effects. However, there is no officially approved MSC therapy for SLE worldwide so far. Most studies are still under clinical investigation. Indeed, clinical therapeutic inconsistency might be a major impediment to their clinical application, which may be due to the involvement of different tissue-derived MSCs, appropriate dose of infused cells, and dosing frequency, although a good safety profile of MSC therapy has been largely certified in clinical trials [94–96]. Further attempts will be focused on distinguishing the biological properties and functions of MSCs derived from different tissues, establishing an optimal culturing system for rapid expansion of MSC, and producing potent lesion-directed functional MSC against inflammatory cytokine.

Precision medicine in SLE

Precision medicine in SLE is highly complex, requiring a personalized approach across diagnosis, treatment, and management. As outlined in Table 3 using the 2019 EULAR/ACR classification criteria, SLE exhibits diversity in clinical manifestations, serology, and underlying immunological mechanisms [97]. Standardized criteria aid in identifying patient populations with shared characteristics, facilitating targeted research and personalized treatments. Omic technologies differentiate treatment-sensitive from resistant SLE patients by identifying genetic and molecular distinctions. Precision SLE treatment customizes interventions based on personalized diagnosis and genetics, improving outcomes and quality of life while minimizing side effects.

Conclusions and further perspectives

SLE remains a complex autoimmune disease with diverse multi-systemic manifestations, posing significant challenges for clinicians, patients, and researchers in identifying specific therapy targets. While no cure exists for SLE, significant progress has been made in its treatment. This includes promising developments in antibody-targeted therapies and orally administered drugs like Voclosporin for SLE and LN. In this review, we have presented an overview of current and past antibody-targeted therapeutic approaches in the

Table 1: Current approved-immunotherapy for systemic lupus erythematosus (SLE).

Brand	Targets	Sponsor	Nation	Indications	Years
Benlysta	B-cell activating factor (BAFF)	GlaxoSmithKline	US	Active lupus in adults	2011
				Lupus in children	2019
				Adult patients with active LN	2020
				Children ages 5 and older with active LN	2022
Saphnelo	Type I interferon (IFN-I)	AstraZeneca	US	Adults with moderate to severe lupus	2021
Telitacicept	BAFF and a proliferation-inducing ligand (APRIL)	RemeGen Co.,Ltd	China	Lupus in adults	2021

APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; IFN-I, type 1 interferon; LN, lupus nephritis.

Table 2: Emerging biological therapy for systemic lupus erythematosus (SLE) treatment.

Drug/ Code	Target	Indications	Status	NCT
KP-104	Complement-targeted	PNH; SLE-TM	Phase II	NCT05504187
Daxdilimab	ILT7	DLE; LN; SLE	Phase II	NCT05591222
Litifilimab	BCDA2	SLE	Phase III	NCT05352919
Itolizumab	CD6	SLE	Phase I	NCT04128579
Rigerimod	Peptides-targeted	SLE	Phase III	NCT02504645

BCDA, blood dendritic cell antigen; CD, cluster of differentiation; DLE, discoid lupus erythematosus; ILT, immunoglobulin-like transcript; LN, lupus nephritis; PNH, paroxysmal nocturnal hemoglobinuria; SLE-TM, SLE associated with thrombotic microangiopathy.

Table 3: Prospective strategies for tailored therapy based on precision methods.

Steps	Contents	Reference
Clinical phenotype	Malar rash, photosensitivity, discoid rash, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, antinuclear antibodies, immunologic disorders.	[97]
Personalized diagnosis	(1) Multi-omic analysis detects genetic variations and molecular patterns in SLE individuals. (2) Clinical data and patient history aid precise diagnosis.	[98]
Precision therapeutics	(1) Targeted treatments focus on immune pathways and molecular targets specific to different SLE subtypes. (2) Genetic and molecular profiling guides treatment strategies, optimizing therapy effectiveness and minimizing side effects.	[99, 100]

treatment of SLE, and have proposed several potential future therapeutic strategies for SLE.

It has become evident that abnormal B cell function, T cell dysfunction, complementary system dysregulation, and inflammation-driven pathology are potential targets for SLE therapy. Notably, sirolimus, also known as rapamycin, is an immunosuppressive medication that has been investigated for its potential role in treating SLE through inhibiting mTOR signaling pathway, reducing the activity of immune cells, and thereby slowing down inflammatory responses and autoimmune attacks [101, 102]. Recently, treating active SLE patients with sirolimus improves disease activity, increases Tregs, and suppresses IL-4 and IL-17 generation without safety concerns [103]. Furthermore, sirolimus exhibited comparable efficacy to both tacrolimus and MMF in treating SLE or LN patients, while demonstrating superior results in terms of serological enhancements and glucocorticoid reduction based on the real world Chinese SLE Treatment and Research group (CSTAR) cohort studies. Crucially, sirolimus was well-tolerated among SLE patients [104, 105]. However, the use of sirolimus requires caution, as it can lead to certain side effects and immune suppression, necessitating clinical monitoring. More research is needed to confirm sirolimus's effectiveness for treating SLE. Notably, CSTAR is committed to raising awareness among Chinese SLE patients, providing crucial clinical insights, optimizing treatment strategies, and offering evidence-based references for informed policy decisions.

Proper animal models play a critical role in assessing the preclinical efficacy and safety of new therapies before human trials. There is no ideal animal model for evaluating fully humanized antibody efficacy in SLE. Despite challenges in creating appropriate models for biologics, organoids derived from tissue-specific progenitor cells of SLE patients, such as kidney and skin tissue, show promise for understanding SLE mechanisms [77, 106]. Likewise, upcoming

technologies like organs-on-chip, artificial intelligence (AI) advancements, and CRISPR-Cas9 genome editing will greatly influence our understanding of SLE's causes, biomarker identification, and the progress of diagnosis and treatment.

Epigenetics research has led to novel drugs for SLE, with microRNA (miRNA) dysfunction in immune cells contributing to the disease. miR-146 and miR-155 have garnered substantial attention for their contributions to disease development, and they are notably elevated in the plasma of SLE patients [107]. miR-146 functions as a negative regulator of innate immune signaling in DCs, specifically targeting genes within TLR pathways. Conversely, miR-155 is upregulated in B cells, driving autoantibody production and inflammatory pathway activation [108–110]. While miRNA-targeting therapies have not been approved for SLE yet, miRNA-based treatments show promise due to advantages like quick production, cost-effectiveness, and potential for oral administration, suggesting significant market potential [111].

Last, exploring multiple therapy combinations for optimized clinical benefits while ensuring safety are the avenue to be explored. Currently, the treat-to-target approach, aiming for clinically effective treatment endpoints, is crucial in SLE clinical trial design and future medical strategies. The success of belimumab and anifrolumab stems from stringent entry criteria and the SRI-4 measurement, yielding more impactful outcomes. Novel SLE therapies demand thoughtful consideration of targets, druggable properties, dosing, safety, patient enrollment, clinical efficacy assessment, and risk-benefit analysis.

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