Rheumatology and Orthopedic Medicine

Review Article ISSN: 2399-7370

Progress and prospects of biologics and small molecules for the treatment of patients with systemic lupus erythematosus

Xiaoquan Wei and Huaxiang Liu*

Department Rheumatology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong Province, 250012, China

Abstract

Due to the complexity of the pathogenesis of systemic lupus erythematosus (SLE), the research and development of drugs targeting different pathogenesis or targets of SLE and their application in clinical treatment will be a major topic at present and in the future. According to the existing viewpoints and the latest research results from basic to clinical, new breakthroughs may occur in the research, development, and application of drugs, including drugs targeting B cells, T cells, long-lived plasma cells (LLPCs), neutrophils, type I interferons (IFN-I) and its signal system, plasmacytoid dendritic cell-specific receptor (PDCSR), interleukin (IL)-12 and IL-23. There are also immune complex blockers and small molecular compounds. The new developed cereblon modulator iberdomide which targets transcription factor Ikaros and Aiolos is also included. Based on these backgrounds, this review not only expounds the research and development of various new biological agents and small molecular compounds, but also prospects their developmental and therapeutic direction, in order to provide a valuable reference for the new progress or breakthrough in the treatment of SLE.

Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous disease with complex pathogenesis, which involves many aspects, such as abnormal B cell function, T cell dysfunction, neutrophil dysfunction, abnormal production and response of type I interferons (IFN-I). It is difficult to effectively treat SLE by acting on a pathogenic factor or signal pathway [1-4]. Although many therapeutic targets for the above pathogenesis have been recognized, which pathogenesis is embodied in which aspects of SLE and the exact degree of SLE need to be further explored. Although the application of biological agent belimumab has made new progress in improving the condition of SLE, there is still a big gap compared with the goal of successful treatment of SLE [1]. In terms of therapeutic drugs for SLE, it is now in a new era when a variety of new biological agents and small molecular compounds are being developed and clinical trials are being carried out. Based on these backgrounds, this review not only expounds the research and development of various new biological agents and small molecular compounds, but also prospects their developmental and therapeutic direction, in order to provide a valuable reference for the new progress or breakthrough in the treatment of SLE.

Targeting B cells in SLE

B cells are not only antibody secreting cells, antigen-presenting cells and T cell helper cells, but also their pluripotency is reflected in the release of cytokines to regulate other immune cells [5]. B cells exert a prominent contribution to the pathogenesis of SLE [1,6-8]. B cell-targeted therapies have been suggested as a new rational approach for SLE treatment [9]. Targeting B cells constitutes the major focus in recent clinical trials [3]. In the future, further understanding the B cell signals underlying breaks in tolerance, the relative contributions of extrafollicular (EF)-dependent versus germinal center (GC)-dependent B cell activation in SLE pathogenesis, and the role of B cell memory in disease maintenance will help to formulate safe and effective new strategies for the treatment of SLE [8].

Biologics targeting B cell growth and survival signals

Belimumab

Belimumab is a fully humanized monoclonal antibody targeting B cell-activating factor (BAFF) or B-lymphocyte stimulator (BLyS) and is the first and the only biological agent approved for treatment of SLE in over 50 years [10]. It has been shown to reduce autoantibody levels in patients with SLE and help control disease activity [11]. Belimumab is approved in over 75 countries for the treatment of adults with SLE. Efficacy and safety of belimumab in lupus pregnant women also have been well established [12]. Over the past 10 years, belimumab has established its position as a disease modifier in the SLE treatment paradigms [13]. It is believed that belimumab will be more widely used for a long time in the future.

Blisibimod

Blisibimod is a potent and selective BAFF inhibitor composed of a tetram-eric BAFF binding domain fused to a human IgG1 Fc region. In a phase III trial, reductions in SLE autoantibodies and B cells, and

Correspondence to: Huaxiang Liu, Department Rheumatology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong Province, 250012, China, E-mail: lzzlhx63@163.com or huaxiangliu@hotmail.com

Key words: *systemic lupus erythematosus, biologics, small molecules, B cells, T cells, neutrophils, type I interferons*

Received: December 08, 2021; **Accepted:** December 17, 2021; **Published:** December 30, 2021

increases in complement C3 and C4 were observed after blisibimod treatment. Although the SRI-6 end point was not met, blisibimod was associated with successful steroid reduction, decreased proteinuria and biomarker responses [14]. It is hoped that further phase III trials on blisibimod in SLE will highlight its potential role in the management of this intractable disease [15].

Telitacicept

Telitacicept (RC18) is a recombinant TACI-Fc fusion protein targeting both BLyS and APRIL at the meantime. The efficacy and safety of telitacicept versus placebo under the background of standard therapy were evaluated in a phase IIb trial in patients with SLE. This trial succeeded in meeting the primary endpoint of Systemic Lupus Erythematosus Responder Index (SRI)-4 and validating its safety [16,17]. Telitacicept has been approved by National Medical Products Administration (MNPA) for the treatment of patients with SLE in China [18].

Biologics targeting B cell surface antigens

Biologics targeting CD20

CD20 is an activated-glycosylated phosphoprotein only expressed on B cells from pre-B cells to memory B cells, but not expressed neither by pro-B cells, antibody-producing plasma cells or T cells. Thus, targeting CD20 spares the B cell precursor, pro-B cells and plasma cells, removing the autoreactive memory B cells and reconstituting the population of naïve transitional B cells [6]. The encouraging results from the recent studies on fully humanized anti-CD20 antibodies offer the prospect of a real revolution in the treatment of SLE [19].

Rituximab

Rituximab is an anti-CD20 chimeric monoclonal antibody and has obvious curative effect on B cell depletion in SLE therapy [20]. However, rituximab failed to achieve primary endpoints in two clinical trials despite multiple observational and retrospective studies showing its beneficial effect on SLE [9]. Although the efficacy of rituximab is highly controversial for SLE, a meta-analysis provides clear beneficial effects of it in patients with lupus nephritis [21]. Therefore, rituximab is recommended to treat refractory lupus nephritis. Besides, existing studies on the combination of belizumab and rituximab have shown that the combination of belizumab and rituximab is more effective than standard belizumab [9,22-24]. The combined drug treatment strategies may change the current treatment paradigms. The patients with SLE will more effective and less toxic therapy. Ultimately, combined approaches targeting both innate and adaptive arms of the immune system and an improved understanding of disease heterogeneity may be needed to provide relief to patients with this intractable disease [8].

Ocrelizumab

Ocrelizumab is a fully humanized monoclonal antibody against CD20, with higher antibody-dependent cellular cytotoxicity (ADCC) activity and lower complement-dependent cytotoxicity (CDC) effects compared to rituximab in SLE patients. In the two-phase III clinical trials, they were terminated prematurely due to the high incidence of serious infections and no additional benefit to SLE, respectively [25].

Ofatumumab

Ofatumumab is a fully humanized IgG1κ anti-CD20 monoclonal antibody. It can be used as an effective substitute for rituximab in allergic patients, but so far, no active clinical trial has been conducted to study its safety and efficacy [25].

Obinutuzumab

Obinutuzumab is a new generation, glycoengineered type II anti-CD20 monoclonal antibody. Obinutuzumab is more effective at evoking Fcγ receptor-mediated effector mechanisms as compared with rituximab. It was superior to rituximab at inducing B-cell depletion [26]. More clinical trials are needed to confirm its availability in clinical application in the future.

Biologics targeting CD22

CD22 is a B-cell-restricted membrane co-receptor expressed on the surface of pro-B cell. It is present throughout the most of B cell development, highly expressed on naïve B cells, but not expressed on plasma blasts and plasma cells [6]. Epratuzumab is a humanized IgG1 monoclonal antibody that targets CD22 resulting in selective B cell modulation [27]. It has been extensively studied for SLE. Epratuzumab may be relatively safe and may have better therapeutic effectiveness than placebo control conditions in patients with SLE [28]. Epratuzumab treatment improved the SLE disease activity in patients with SLE and associated Sjögren's syndrome [29]. At present, there is not clear evidence to prove the clinical efficacy of epratuzumab.

Biologics targeting CD19

CD19 is a transmembrane glycoprotein of the Ig superfamily which is expressed throughout the whole B cells development from the pre-B cells to the plasma cells [6]. Targeting CD19 could provide a more comprehensive depletion of B cells and plasma cells in patients with SLE. Obexelimab, as a humanized anti-CD19 monoclonal antibody, can make the depletion of B cells and plasma cells more competely. Due to the phase II clinical trial failed to reach the primary endpoint, its prospect in the treatment of SLE is not optimistic [25].

Drugs affecting T cell activity

T cells play a central role in pathogenesis of SLE. T cell dysregulation has been implicated in the loss of tolerance and overactivation of B cells in SLE. Recent studies have identified T cell subsets and genetic, epigenetic, and environmental factors that contribute to pathogenic T cell differentiation, as well as disease pathogenesis and clinical phenotypes in SLE [30].

Low-dose interleukin-2

The cytokine interleukin-2 (IL-2) is essentially required for the growth and survival of regulatory T cells (Treg) which are crucial for the maintenance of peripheral tolerance and for the control of ongoing inflammation and autoimmunity. Low-dose IL-2 therapy aims either to compensate for the IL-2 deficiency to restore a physiological state or to strengthen the Treg population in order to be more effective in counter-regulating inflammation while avoiding global immunosuppression [31]. Low-dose IL-2 therapy can promote the selective expansion of a functionally competent Treg population in a well-tolerated way and may have the potential to influence the clinical course in patients with active SLE [32]. A randomized, double-blind, and placebo-controlled clinical trial of low-dose interleukin-2 (IL-2) in treatment of SLE showed that low-dose IL-2 may sustain cellular immunity with enhanced natural killer cells, as well as expansion of regulatory T cells [33]. Low-dose IL-2 therapy can recover T follicular regulatory (Tfr) and T follicular (Tfh) immune balance [34]. A good response was achieved in patients with lower regulatory T cells (Treg) proportion and skin rash in SLE patients with low-dose IL-2 treatment [35]. Low dose of IL-2 combined with rapamycin was able to restore the number

of Treg and the balance of Th17/Treg cells. This approach was able to induce immune tolerance and promote disease remission, allowing for the reduction in prednisone dosage [36]. Furthermore, Low-dose IL-2 prolonged treatment can alleviate pathogenic humoral immunity and improve renal function [37]. Further study of T cell subsets and biomarkers of T cell action may pave the way for specific targeting of pathogenic T cell populations in SLE [30].

Selective T cell costimulatory regulator

Abatacept has demonstrated efficacy in other autoimmune diseases, but in SLE, randomized clinical trials have failed to achieve their primary outcome. Despite these disappointing results and based on its mechanism of action, abatacept seems to have a role in lupus nephritis and arthritis [38]. Different responsiveness of abatacept was observed in different disease severity which was segmented by immune cell clustering [39]. Some efficacy of abatacept was observed in patients with SLE refractory to conventional treatment in routine clinical practice, particularly in the case of articular manifestations, with an acceptable safety profile. New controlled trials of abatacept in SLE patients should be conducted in future [40].

Post-translational modifications in T Cells

Protein post-translational modifications (PTMs) have been emphasized for their roles in activating protein activity, maintaining structural stability, regulating protein-protein interactions and mediating signaling pathways, in addition to other biological functions. Abnormal signal transduction pathways are usually mediated by phosphorylation and dephosphorylation, which has been considered to be the main cause of T cell dysfunction in the pathogenesis of SLE. The proliferation, polarization, adhesion, and migration of T cells in SLE patients are also regulated by phosphorylation. Because a variety of kinases and phosphatases are involved in the regulation of abnormal T cell function in the pathogenesis of SLE and the interaction between these enzymes, it is difficult to select a kinase as the therapeutic target of SLE. The precise mechanism between T cell function and abnormal cell surface glycosylation pattern in SLE remains to be further clarified. Protein methylation is involved in the pathogenesis of SLE. Methylation modification plays a key role in mediating T cell activation. However, the characteristics of methyltransferases or demethylases mediating its process have not been fully investigated. Acetylation is commonly regulated by acetyltransferases and deacetylases and is increasingly considered an important regulatory modification process in SLE pathogenesis. The ubiquitination is an important regulatory component of the Th17 cell function in SLE. There has been little research on the role of deubiquitination in the regulation of T cell dysfunction in SLE. Now, no direct related research focuses on the regulating role of SUMOylation on SLE T cell function. In summary, by studying the potential role of different PTMs in regulating the function and signaling pathways of T cells in the pathogenesis of SLE, it is possible to discover or identify or establish new targets for SLE therapy [41].

Co-stimulation blockade

Co-stimulatory and co-inhibitory molecules control interactions between B and T cells during an inflammatory response, which is essential for an appropriate host protection and maintenance of self-tolerance. Dampening immune responses by either blocking co-activating signals or enhancing co-inhibitory signals in different cell types is a promising approach to treat SLE to better control active disease but may also allow resolution of chronic autoimmunity [5]. B cell immune stimulation interacts with T cells and antigen-presenting cells through co-stimulatory signals. Rigerimod prevents antigen presentation to auto-reactive T cells, thereby preventing B cell maturation. Several phase II trials in patients with SLE showed that rigerimod could significantly reduce disease activity. CD40 ligand (CD40L) binds to CD40 of antigen-presenting cells and B cells, which induces co-stimulation and promote B cell maturation. Different clinical trials show that although CD40L has no serious side effects, its efficacy has different results, and its effectiveness needs to be further confirmed [1].

Drugs targeting long-lived plasma cells

Long-lived plasma cells (LLPCs) are pathogenic in SLE. These cells still secrete autoantibodies when treated with immunosuppressive agents and B cell targeting drugs, thereby they can be considered as therapeutic targets. Because LLPCs highly express CD38, the therapeutic potential of daratumab (which can target CD38) in 2 patients with life-threatening lupus (refractory lupus nephritis and autoimmune hemolytic anemia) was studied. After daratumab administration, 2 patients had good clinical and serological responses. These effects were related to the significant deletion of LLPCs, the decrease of IFN-I activity, and the downregulation of T cell transcription associated with chronic inflammation [42]. The exact efficacy of daratumab on SLE patients remains to be confirmed by clinical trials. A better understanding of LLPCs in disease chronicity may inform the development of safe and effective therapies for SLE in future [8].

Relationship between neutrophil target and SLE

In SLE disease, neutrophil dysregulation is characterized by impaired phagocytosis, reduced ability to recognize and remove dead cells, and abnormalities of various metabolic pathways. Neutrophils are an important source of IFN-I. Through the in-depth study of neutrophil extracellular traps (NETs), we have a deeper understanding of neutrophils in the pathogenesis of SLE. Some genetic polymorphisms associated with the risk of SLE may be related to neutrophil dysregulation, which is characterized by enhanced formation of NETs. Furthermore, many SLE patients have impairments in NET clearance. Neutrophil dysregulation affects the innate immune response and adaptive immune response of SLE. It is expected to find new potential therapeutic targets from these pathogenic mechanisms. A series of in vivo and in vitro experimental studies and clinical trials on inhibiting the formation of NETs show its effective therapeutic effect, which may reduce subsequent disease flares in patients with SLE with low disease activity [2]. Further study on the mechanism of neutrophil dysregulation in SLE is expected to provide new targets on aberrant neutrophil subsets for the treatment of SLE patients.

Drugs targeting IFN-I and its signal pathway

Recent translational research discoveries of the importance of the dysregulation of the innate immune system in SLE have led to clinical trials that target IFN [43,44]. IFN-I plays a central role in the pathogenesis of SLE [2]. In recent 10 years, one of the key findings to accelerate and deepen the understanding of the pathogenesis of SLE is to recognize that the level of IFN-I signature elevation in SLE patients, and the abnormal production and response of IFN-I is a landmark feature of SLE [4]. It is proposed that down-regulation of IFN-regulated gene expression (the IFN signature) lessen the clinical burden of SLE [43,45]. Therefore, targeting of IFN-I and of its downstream pathways has emerged as important developments for novel drug research in SLE [44]. Now, several SLE therapeutic drugs targeting IFN-I and its signal pathway are being developed. The safety and effectiveness of various

new therapeutic drugs targeting IFN-I and its signal pathway showed broad development prospects.

Anifrolumab

Anifrolumab is a monoclonal antibody against IFN-I receptor, which antagonizes effects of all type of IFN-I (IFNα, IFNβ, IFNω, and IFNκ) [46]. Anifrolumab shows promise as an addition to the SLE therapeutic armamentarium [47]. A phase IIb clinical trial showed that it can significantly reduce the disease activity of patients with moderate to severe SLE at multiple clinical endpoints [48]. Pooled data from the phase II and III trials showed that anifrolumab reduces flares while permitting glucocorticoid taper in patients with SLE [49-52]. Long-term anifrolumab treatment demonstrates an acceptable safety profile with sustained improvement in SLE disease activity, health-related quality of life, and serologic measures [53].

Anti-interferon antibodies

Sifalimumab

The efficacy and safety of sifalimumab were evaluated in a phase IIb, randomised, double-blind, placebo-controlled study of adults with moderate to severe active SLE. At different clinical endpoints, the improvement of the activity of the overall disease and the degree of damage to the affected organs was consistent. These beneficial results indicated that sifalimumab is a promising treatment for adults with SLE [54]. It is proposed that anti-interferon therapy with sifalimumab could be an alternative treatment for pediatric patients with severe interferon mediated SLE in the future [55].

Rontalizumab

Rontalizumab is a humanized IgG1 anti-IFN-α monoclonal antibody. The efficacy and safety of rontalizumab in patients with moderate to severe active SLE were assessed. Rontalizumab is not effective for all SLE patients in the primary and secondary end points. Subgroup analysis revealed a favorable response in patients with low interferon signatures, but no response in patients with high interferon signatures [56].

JNJ-55920839

JNJ-55920839 is a fully human immunoglobulin G1κ antibody targeting IFNα/ω. The investigation of pharmacokinetics and pharmacodynamics of JNJ-55920839 showed that increases in total IFNα/ω levels were observed in both healthy subjects and SLE patients after JNJ-55920839 treatment [57]. Furthermore, two gene signatures (IFN-I Signaling and Immunoglobulin Immune Response) exhibited pharmacodynamic changes among JNJ-55920839 responders, which suggested that these signatures may enable enrichment for treatment responders when using IFN-I-suppressing treatments in SLE [58].

IFNα kinoid

IFNα kinoid is an inactivated recombinant human IFNα2b vaccine. IFNα kinoid can induce neutralising anti-IFN-α2b antibodies and significantly reduce the IFN gene signature. IFNα kinoid induces a polyclonal anti-IFNα response that decreases IFN- and B cell-associated transcripts [59]. Although the clinical coprimary endpoint was not met in a phase IIb trial, relevant secondary endpoints were achieved after IFNα kinoid treatment in patients with SLE with moderate to severe disease activity and positive interferon (IFN) gene signature. It deserves further assessment in phase III trials in future [60].

Drugs targeting plasmacytoid dendritic cell-specific receptor

BIIB059 is a humanized IgG1 monoclonal antibody that binds a plasmacytoid dendritic cell receptor (blood dendritic cell antigen 2, BDCA2), and results in the inhibition of production of IFN-I and additional inflammatory cytokines. The establishment of the clinical population pharmacokinetic (PK) and pharmacodynamic (PD) model for BIIB059 in phase 1 PK/PD study of healthy adult volunteers and SLE subjects provides valuable insight into the dynamics and dose-response relationship of BIIB059 for the treatment of SLE [61]. BIIB059 decreased IFN expression and improved cutaneous lupus disease activity, with a favorable safety profile in an intriguing phase 1b study [62,63]. In a phase II trial, the total number of active joints improved significantly with BIIB059 treatment compared with the placebo control group [3].

Drugs yargeting IL-12 and IL-23

Ustekinumab is a monoclonal antibody against P40 of IL-12 and IL-23. The efficacy and safety of ustekinumab was evaluated in a phase II trial in patients with moderate to severe SLE, excluding lupus nephritis and central nervous system lupus. Ustekinumab provided sustained clinical benefit in patients with SLE through 1 year, with a safety profile consistent with other indications [64]. The latest phase II clinical study showed that IL-12 blockade has an important role in the mechanism of action of ustekinumab treatment in patients with SLE [65].

Blockers of immune complexes

Negative signaling by Fcγ receptor (FcγR) IIB is mainly important for the regulation of activated B cells. SLE patients have a lower expression of FcγRIIB. FcγRIIB was chosen as a therapeutic target because of its limited human polymorphism and lack of immunogenicity. SM101 is an extracellular version of the human FcγRIIB. It binds to immune complex (IC) in SLE and blocks the Fcγ-mediated signal. A phase IIa trial in SLE patients showed that the results seem promising [1].

Cereblon modulator

Transcription factors Ikaros and Aiolos are critical for B cell differentiation which are implicated in the pathogenesis of SLE, targeting them with the cereblon modulator iberdomide has been proposed as a promising therapeutic agent. Iberdomide has been shown to inhibit the activation and differentiation of B cells and modulate the gene expression in differentiating plasmablasts from SLE patients, thus supporting the therapeutic targeting of Ikaros family transcription factors in SLE and potentially other autoimmune conditions [66]. A phase 1 healthy volunteer study and SLE patient cells demonstrated that pharmacodynamic activity of iberdomide supports its further clinical development for the treatment of SLE [67].

Therapeutic potential of small molecules

The potential for therapeutic effects of small molecule inhibition such as Janus kinase (JAK), tyrosine kinase (Tyk), and Bruton's tyrosine kinase (Btk) is now being investigated for treating SLE [3].

JAK inhibitors: Inhibition of the JAK-STAT pathway is an attractive therapeutic option [68]. Selective inhibition of JAK1 leads to a decrease of proinflammatory cytokine expression and reduced immune activation in patients with cutaneous lupus erythematosus [69]. Now, a variety of JAK inhibitors are being developed and tried to be used in the treatment of SLE.

Baricitinib

Baricitinib has potential to fine-tune various immune networks through a variety of mechanisms [70]. The phase II clinical trial of

JAK1/2 inhibitor baricitinib showed that it not only significantly increased the proportion of arthritis or rash relief and improved the signs and symptoms of active SLE in patients [71], but also significantly reduced the RNA expression of gene networks related to JAK/STAT pathway, cytokine signals, and the pathogenesis of SLE [72]. Precision medicine is required in order to achieve maximum effects of baricitinib in the future [70].

Tofacitinib

Tofacitinib is a JAK inhibitor that blocks signaling downstream of multiple cytokines implicated in lupus pathogenesis [73]. A phase I clinical trial of tofacitinib showed that it not only improved cardiometabolic and immunologic parameters associated with the premature atherosclerosis in SLE, but also had good safety and tolerability. Further mechanistic investigation is needed to better characterize the pathways responsible for findings in this study [74].

Tyk2 inhibitors

Tyk2 is a non-receptor tyrosine-protein kinase and is a key component of the JAK-STAT signaling pathway. At present, there are many patents for Tyk2 inhibitors, and it is confirmed that selective Tyk2 inhibitors can effectively provide pharmacological benefits in the treatment of SLE [75,76].

Btk inhibitors

Btk is a non-receptor tyrosine kinase that signals downstream of Fc receptors and plays a transduction role in antibody expression following B cell activation. It is involved in regulating B cell proliferation and survival. Its blockade results in B cell apoptosis [77].

BIIB068

The newly discovered BIIB068 is a potent and reversible Btk inhibitor, which achieved >90% inhibition of Btk phosphorylation in human beings [77].

Ibrutinib

Ibrutinib is a tyrosine kinase selective and irreversible inhibitor. It binds to Btk causing B cell apoptosis [78]. Pre-clinical trials showed that ibrutinib reduced levels of autoantibodies [1].

Fenebrutinib

Fenebrutinib (GDC-0853) is a noncovalent, oral, and highly selective inhibitor of Btk. A phase II trial showed that the primary end point, SRI-4 response, was not met despite evidence of strong pathway inhibition, while fenebrutinib had an acceptable safety profile [79].

Evobrutinib

Evobrutinib is a novel, highly selective, irreversible Btk inhibitor. In the SLE model, evobrutinib inhibited B cell activation, reduced autoantibody production and plasma cell numbers, and normalized B and T cell subsets. It is a promising molecule for the treatment of SLE [80].

Development and application prospect of new biologics and small molecules

The need for more successful biologic or other new therapies remains important as it is clear we have reached the limit of what can be achieved with conventional immunosuppression [1]. In addition to developing new drugs to treat SLE, future trials have to focus on more effective study designs to improve chances of trial success [81]. The emergence of belimumab has filled the gap in biologic therapy, the use of rituximab provides guidance for the treatment of LN, combination of them also brings more options. Besides, it's encouraging that the application of some other biological agents such as telitacicept, ofatumumab and so on shows new promise. Small molecular oral drugs such as baricitinib and tofacitinib may become the mainstream of treatment in SLE. At present, various new biological agents and small molecular compounds have been or are being developed, and clinical trials are being or will be carried out. It is believed that in the near future, a variety of biologics and small molecules targeting different targets or pathogenesis of SLE will be used in clinical practice. With the combined application of different drugs and the formulation of more targeted personalized treatment schemes, it can be expected to maximize the improvement of the condition of SLE patients. We earnestly hope that this time will come earlier.

References

1. Carreira PL, Isenberg DA (2019) Recent developments in biologic therapies for the treatment of patients with systemic lupus erythematosus. *Rheumatology (Oxford)* 58: 382-387. [Crossref]
2. Liu Y, Kaplan MJ (2021) Neutrophil dysregulation in the pathogenesis of systemic lupus erythematosus. *Rheum Dis Clin North Am* 47: 317-333. [Crossref]
3. Sharabi A (2021) Updates on clinical trials in systemic lupus erythematosus. *Curr Rheumatol Rep* 23: 57. [Crossref]
4. Sirobhushanam S, Lazar S, Kahlenberg JM (2021) Interferons in systemic lupus erythematosus. *Rheum Dis Clin North Am* 47: 297-315. [Crossref]
5. Stefanski AL, Dörner T (2021) Immune checkpoints and the multiple faces of B cells in systemic lupus erythematosus. *Curr Opin Rheumatol* 33: 592-597. [Crossref]
6. Lee WS, Amengual O (2020) B cells targeting therapy in the management of systemic lupus erythematosus. *Immunol Med* 43: 16-35. [Crossref]
7. Atisha-Fregoso Y, Toz B, Diamond B (2021) Meant to B: B cells as a therapeutic target in systemic lupus erythematosus. *J Clin Invest* 131: e149095. [Crossref]
8. Canny SP, Jackson SW (2021) B cells in systemic lupus erythematosus: From disease mechanisms to targeted therapies. *Rheum Dis Clin North Am* 47: 395-413. [Crossref]
9. Petricca L, Gigante MR, Paglionico A, Costanzi S, Vischini G, et al. (2020) Rituximab followed by belimumab controls severe lupus nephritis and bullous pemphigoid in systemic lupus erythematosus refractory to several combination therapies. *Front Med (Lausanne)* 7: 553075. [Crossref]
10. Depascale R, Gatto M, Zen M, Saccon F, Larosa M, et al. (2021) Belimumab: a step forward in the treatment of systemic lupus erythematosus. *Expert Opin Biol Ther* 21: 563-573. [Crossref]
11. Singh JA, Shah NP, Mudano AS (2021) Belimumab for systemic lupus erythematosus. *Cochrane Database Syst Rev* 2: CD010668. [Crossref]
12. Kao JH, Lan TY, Lu CH, Cheng CF, Huang YM, et al. (2021) Pregnancy outcomes in patients treated with belimumab: Report from real-world experience. *Semin Arthritis Rheum* 51: 963-968. [Crossref]
13. Levy RA, Gonzalez-Rivera T, Khamashta M, Fox NL, Jones-Leone A, et al. (2021) 10 Years of belimumab experience: What have we learnt? *Lupus* 30: 1705-1721. [Crossref]
14. Merrill JT, Shanahan WR, Scheinberg M, Kalunian KC, Wofsy D, et al. (2018) Phase III trial results with blisibimod, a selective inhibitor of B-cell activating factor, in subjects with systemic lupus erythematosus (SLE): results from a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 77: 883-889. [Crossref]
15. Magro R (2019) Biological therapies and their clinical impact in the treatment of systemic lupus erythematosus. *Ther Adv Musculoskelet Dis* 11: 1759720X19874309. [Crossref]
16. Wu Di, Li J, Xu D, Wang W, Li L, et al. (2019) A human recombinant fusion protein targeting B lymphocyte stimulator (BlyS) and a proliferation-inducing ligand (APRIL), telitacicept (RC18), in systemic lupus erythematosus (SLE): results of a phase 2b study. *Arthritis Rheumatol*: 71.
17. Nie Y, Zhao L, Zhang X (2021) B cell aberrance in lupus: the ringleader and the solution. *Clin Rev Allergy Immunol*. [Crossref]

18. Shi F, Xue R, Zhou X, Shen P, Wang S, et al. (2021) Telitacicept as a BLyS/APRIL dual inhibitor for autoimmune disease. *Immunopharmacol Immunotoxicol* 43: 666-673. [Crossref]

19. Murphy G, Isenberg DA (2020) Biologic therapies for systemic lupus erythematosus: where are we now? *Curr Opin Rheumatol* 32: 597-608. [Crossref]

20. Crickx E, Weill JC, Reynaud CA, Mahévas M (2020) Anti-CD20-mediated B-cell depletion in autoimmune diseases: successes, failures and future perspectives. *Kidney Int* 97: 885-893. [Crossref]

21. Teng S, Tian Y, Luo N, Zheng Q, Shao M, et al. (2021) Efficacy and safety of an anti-CD20 monoclonal antibody, rituximab, for lupus nephritis: A meta-analysis. *Int J Rheum Dis*. [Crossref]

22. Teng YKO, Bruce IN, Diamond B, Furie RA, van Vollenhoven RF, et al. (2019) Phase III, multicentre, randomised, double-blind, placebo-controlled, 104-week study of subcutaneous belimumab administered in combination with rituximab in adults with systemic lupus erythematosus (SLE): BLISS-BELIEVE study protocol. *BMJ Open* 9: e025687.

23. Kraaij T, Arends EJ, van Dam LS, Kamerling SWA, van Daele PLA, et al. (2021) Long-term effects of combined B-cell immunomodulation with rituximab and belimumab in severe, refractory systemic lupus erythematosus: 2-year results. *Nephrol Dial Transplant* 36: 1474-1483.

24. Shipa M, Embleton-Thirsk A, Parvaz M, Santos LR, Muller P, et al. (2021) Effectiveness of belimumab after rituximab in systemic lupus Erythematosus: A randomized controlled trial. *Ann Intern Med.* [Crossref]

25. Bag-Ozbek A, Hui-Yuen JS (2021) Emerging B-cell therapies in systemic lupus erythematosus. *Ther Clin Risk Manag* 17: 39-54. [Crossref]

26. Reddy VR, Pepper RJ, Shah K, Cambridge G, Henderson SR, et al. (2021) Disparity in peripheral and renal B-cell depletion with rituximab in systemic lupus erythematosus: an opportunity for obinutuzumab? *Rheumatology (Oxford)* 11: keab827. [Crossref]

27. Geh D, Gordon C (2018) Epratuzumab for the treatment of systemic lupus erythematosus. *Expert Rev Clin Immunol* 14: 245-258. [Crossref]

28. Li J, Wei MM, Song Q, Guo XH, Shao L, et al. (2019) Anti-CD22 epratuzumab for systemic lupus erythematosus: A systematic review and meta-analysis of randomized controlled trials. *Exp Ther Med* 18: 1500-1506. [Crossref]

29. Gottenberg JE, Dörner T, Bootsma H, Devauchelle-Pensec V, Bowman SJ, et al. (2018) Efficacy of epratuzumab, an anti-CD22 monoclonal IgG antibody, in systemic lupus erythematosus patients with associated Sjögren's syndrome: Post hoc analyses from the EMBODY trials. *Arthritis Rheumatol* 70: 763-773. [Crossref]

30. Paredes JL, Fernandez-Ruiz R, Niewold TB (2021) T cells in systemic lupus erythematosus. *Rheum Dis Clin North Am* 47: 379-393. [Crossref]

31. Graßhoff H, Comdühr S, Monne LR, Müller A, Lamprecht P, et al. (2021) Low-dose IL-2 therapy in autoimmune and rheumatic diseases. *Front Immunol* 12: 648408. [Crossref]

32. Humrich JY, Riemekasten G (2019) Low-dose interleukin-2 therapy for the treatment of systemic lupus erythematosus. *Curr Opin Rheumatol* 31: 208-212. [Crossref]

33. He J, Zhang R, Shao M, Zhao X, Miao M, et al. (2020) Efficacy and safety of low-dose IL-2 in the treatment of systemic lupus erythematosus: a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 79: 141-149. [Crossref]

34. Miao M, Xiao X, Tian J, Zhufeng Y, Feng R, et al. (2021) Therapeutic potential of targeting Tfr/Tfh cell balance by low-dose-IL-2 in active SLE: a post hoc analysis from a double-blind RCT study. *Arthritis Res Ther* 23: 167.

35. Miao M, Li Y, Xu D, Zhang R, He J, et al. (2021) Therapeutic responses and predictors of low-dose interleukin-2 in systemic lupus erythematosus. *Clin Exp Rheumatol*. [Crossref]

36. Zhao C, Chu Y, Liang Z, Zhang B, Wang X, et al. (2019) Low dose of IL-2 combined with rapamycin restores and maintains the long-term balance of Th17/Treg cells in refractory SLE patients. *BMC Immunol* 20: 32. [Crossref]

37. Liang K, He J, Wei Y, Zeng Q, Gong D, et al. (2021) Sustained low-dose interleukin-2 therapy alleviates pathogenic humoral immunity via elevating the Tfr/Tfh ratio in lupus. *Clin Transl Immunology* 10: e1293. [Crossref]

38. Pimentel-Quiroz VR, Ugarte-Gil MF, Alarcón GS (2016) Abatacept for the treatment of systemic lupus erythematosus. *Expert Opin Investig Drugs* 25: 493-499. [Crossref]

39. Bandyopadhyay S, Connolly SE, Jabado O, Ye J, Kelly S, et al. (2017) Identification of biomarkers of response to abatacept in patients with SLE using deconvolution of whole blood transcriptomic data from a phase IIb clinical trial. *Lupus Sci Med* 4: e000206. [Crossref]

40. Danion F, Rosine N, Belkhir R, Gottenberg JE, Hachulla E, et al. (2016) Efficacy of abatacept in systemic lupus erythematosus: a retrospective analysis of 11 patients with refractory disease. *Lupus* 25: 1440-1447. [Crossref]

41. Yang F, Lin J, Chen W (2021) Post-translational modifications in T cells in systemic erythematosus lupus. *Rheumatology (Oxford)* 60: 2502-2516. [Crossref]

42. Ostendorf L, Burns M, Durek P, Heinz GA, Heinrich F, et al. (2020) Targeting CD38 with daratumumab in refractory systemic lupus erythematosus. *N Engl J Med* 383: 1149-1155. [Crossref]

43. Kalunian KC (2016) Interferon-targeted therapy in systemic lupus erythematosus: Is this an alternative to targeting B and T cells? *Lupus* 25: 1097-1101. [Crossref]

44. Chasset F, Arnaud L (2018) Targeting interferons and their pathways in systemic lupus erythematosus. *Autoimmun Rev* 17: 44-52. [Crossref]

45. Rönnblom L (2016) The importance of the type I interferon system in autoimmunity. *Clin Exp Rheumatol* 34: 21-24. [Crossref]

46. Yu T, Enioutina EY, Brunner HI, Vinks AA, Sherwin CM (2017) Clinical pharmacokinetics and pharmacodynamics of biologic therapeutics for treatment of systemic lupus erythematosus. *Clin Pharmacokinet* 56: 107-125. [Crossref]

47. Goulden B, Isenberg D (2021) Anti-IFNαR Mabs for the treatment of systemic lupus erythematosus. *Expert Opin Biol Ther* 21: 519-528. [Crossref]

48. Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, et al. (2017) Anifrolumab, an anti-interferon-α receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. *Arthritis Rheumatol* 69: 376-386. [Crossref]

49. Anderson E, Furie R (2020) Anifrolumab in systemic lupus erythematosus: current knowledge and future considerations. *Immunotherapy* 12: 275-286. [Crossref]

50. Furie R, Morand EF, Askanase AD, Vital EM, Merrill JT, et al. (2021) Anifrolumab reduces flare rates in patients with moderate to severe systemic lupus erythematosus. *Lupus* 30: 1254-1263. [Crossref]

51. Tanaka Y, Tummala R (2021) Anifrolumab, a monoclonal antibody to the type I interferon receptor subunit 1, for the treatment of systemic lupus erythematosus: an overview from clinical trials. *Mod Rheumatol* 31: 1-12. [Crossref]

52. Tummala R, Abreu G, Pineda L, Michaels MA, Kalyani RN, et al. (2021) Safety profile of anifrolumab in patients with active SLE: an integrated analysis of phase II and III trials. *Lupus Sci Med* 8: e000464. [Crossref]

53. Chatham WW, Furie R, Saxena A, Brohawn P, Schwetje E, et al. (2021) Long-term safety and efficacy of anifrolumab in adults with systemic lupus erythematosus: Results of a phase II open-label extension study. *Arthritis Rheumatol* 73: 816-825. [Crossref]

54. Khamashta M, Merrill JT, Werth VP, Furie R, Kalunian K, et al. (2016) Sifalimumab, an anti-interferon-α monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 75: 1909-1916. [Crossref]

55. Trindade VC, Carneiro-Sampaio M, Bonfa E, Silva CA (2021) An update on the management of childhood-onset systemic lupus erythematosus. *Paediatr Drugs* 23: 331-347. [Crossref]

56. Kalunian KC, Merrill JT, Maciuca R, McBride JM, Townsend MJ, et al. (2016) A Phase II study of the efficacy and safety of rontalizumab (rhuMAb interferon-α) in patients with systemic lupus erythematosus (ROSE). *Ann Rheum Dis* 75: 196-202. [Crossref]

57. Yao Z, Loggia L, Fink D, Chevrier M, Marciniak S, et al. (2020) Pharmacokinetics and pharmacodynamics of JNJ-55920839, an antibody targeting interferon α/ω, in healthy subjects and subjects with mild-to-moderate systemic lupus erythematosus. *Clin Drug Investig* 40: 1127-1136. [Crossref]

58. Seridi L, Cesaroni M, Orillion A, Schreiter J, Chevrier M, et al. (2021) Novel signatures associated with systemic lupus erythematosus clinical response to IFN-α/-ω inhibition. *Lupus* 30: 795-806. [Crossref]

59. Ducreux J, Houssiau FA, Vandepapelière P, Jorgensen C, Lazaro E, et al. (2016) Interferon α kinoid induces neutralizing anti-interferon α antibodies that decrease the expression of interferon-induced and B cell activation associated transcripts: analysis of extended follow-up data from the interferon α kinoid phase I/II study. *Rheumatology (Oxford)* 55: 1901-1905. [Crossref]

60. Houssiau FA, Thanou A, Mazur M, Ramiterre E, Gomez Mora DA, et al. (2020) IFN-α kinoid in systemic lupus erythematosus: results from a phase IIb, randomised, placebo-controlled study. *Ann Rheum Dis* 79: 347-355. [Crossref]

61. Hartmann S, Biliouris K, Naik H, Rabah D, Stevenson L, et al. (2020) A clinical population pharmacokinetic/pharmacodynamic model for BIIB059, a monoclonal antibody for the treatment of systemic and cutaneous lupus erythematosus. *J Pharmacokinet Pharmacodyn* 47: 255-266. [Crossref]

62. Chaichian Y, Wallace DJ, Weisman MH (2019) A promising approach to targeting type 1 IFN in systemic lupus erythematosus. *J Clin Invest* 129: 958-961. [Crossref]

63. Furie R, Werth VP, Merola JF, Stevenson L, Reynolds TL, et al. (2019) Monoclonal antibody targeting BDCA2 ameliorates skin lesions in systemic lupus erythematosus. *J Clin Invest* 129: 1359-1371. [Crossref]

64. van Vollenhoven RF, Hahn BH, Tsokos GC, Lipsky P, Fei K, et al. (2020) Maintenance of efficacy and safety of ustekinumab through one year in a phase II multicenter, prospective, randomized, double-blind, placebo-controlled crossover trial of patients with active systemic lupus erythematosus. *Arthritis Rheumatol* 72: 761-768. [Crossref]

65. Cesaroni M, Seridi L, Loza MJ, Schreiter J, Sweet K, et al. (2021) Suppression of serum interferon-γ levels as a potential measure of response to ustekinumab treatment in patients with systemic lupus erythematosus. *Arthritis Rheumatol* 73: 472-477. [Crossref]

66. Rivellese F, Manou-Stathopoulou S, Mauro D, Goldmann K, Pyne D, et al. (2021) Effects of targeting the transcription factors Ikaros and Aiolos on B cell activation and differentiation in systemic lupus erythematosus. *Lupus Sci Med* 8: e000445. [Crossref]

67. Schafer PH, Ye Y, Wu L, Kosek J, Ringheim G, et al. (2018) Cereblon modulator iberdomide induces degradation of the transcription factors Ikaros and Aiolos: immunomodulation in healthy volunteers and relevance to systemic lupus erythematosus. *Ann Rheum Dis* 77: 1516-1523.

68. Mok CC (2019) The Jakinibs in systemic lupus erythematosus: progress and prospects. *Expert Opin Investig Drugs* 28: 85-92. [Crossref]

69. Fetter T, Smith P, Guel T, Braegelmann C, Bieber T, et al. (2020) Selective Janus kinase 1 inhibition is a promising therapeutic approach for lupus erythematosus skin lesions. *Front Immunol* 11: 344. [Crossref]

70. Kubo S, Nakayamada S, Tanaka Y (2019) Baricitinib for the treatment of rheumatoid arthritis and systemic lupus erythematosus: a 2019 update. *Expert Rev Clin Immunol* 15: 693-700. [Crossref]

71. Wallace DJ, Furie RA, Tanaka Y, Kalunian KC, Mosca M, et al. (2018) Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet* 392: 222-231. [Crossref]

72. Dörner T, Tanaka Y, Petri MA, Smolen JS, Wallace DJ, et al. (2020) Baricitinib-associated changes in global gene expression during a 24-week phase II clinical systemic lupus erythematosus trial implicates a mechanism of action through multiple immune-related pathways. *Lupus Sci Med* 7: e000424. [Crossref]

73. Furumoto Y, Smith CK, Blanco L, Zhao W, Brooks SR, et al. (2017) Tofacitinib ameliorates murine lupus and its associated vascular dysfunction. *Arthritis Rheumatol* 69: 148-160. [Crossref]

74. Hasni SA, Gupta S, Davis M, Poncio E, Temesgen-Oyelakin Y, et al. (2021) Phase 1 double-blind randomized safety trial of the Janus kinase inhibitor tofacitinib in systemic lupus erythematosus. *Nat Commun* 12: 3391. [Crossref]

75. He X, Chen X, Zhang H, Xie T, Ye XY (2019) Selective Tyk2 inhibitors as potential therapeutic agents: a patent review (2015-2018). *Expert Opin Ther Pat* 29: 137-149. [Crossref]

76. Gallucci S, Meka S, Gamero AM (2021) Abnormalities of the type I interferon signaling pathway in lupus autoimmunity. *Cytokine* 146: 155633. [Crossref]

77. Ma B, Bohnert T, Otipoby KL, Tien E, Arefayene M, et al. (2020) Discovery of BIIB068: A selective, potent, reversible bruton's tyrosine kinase inhibitor as an orally efficacious agent for autoimmune diseases. *J Med Chem* 63: 12526-12541.

78. Lorenzo-Vizcaya A, Fasano S, Isenberg DA (2020) Bruton's tyrosine kinase inhibitors: A new therapeutic target for the treatment of SLE? *Immunotargets Ther* 9: 105-110. [Crossref]

79. Isenberg D, Furie R, Jones NS, Guibord P, Galanter J, et al. (2021) Efficacy, safety, and pharmacodynamic effects of the Bruton's tyrosine kinase inhibitor fenebrutinib (GDC-0853) in systemic lupus erythematosus: Results of a phase II, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol* 73: 1835-1846. [Crossref]

80. Haselmayer P, Camps M, Liu-Bujalski L, Nguyen N, Morandi F, et al. (2019) Efficacy and pharmacodynamic modeling of the BTK inhibitor evobrutinib in autoimmune disease models. *J Immunol* 202: 2888-2906. [Crossref]

81. Narain S, Furie R (2016) Update on clinical trials in systemic lupus erythematosus. *Curr Opin Rheumatol* 28: 477-487. [Crossref]