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Drugs in early clinical development for Systemic Lupus Erythematosus

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Abstract

Introduction—While immunosuppressive therapy has positively impacted the prognosis of systemic lupus erythematosus (SLE), many patients still do not respond to traditional therapy. Thus, active SLE disease remains a significant problem. Furthermore, conventional immunosuppressive treatments for SLE are associated a high risk of side effects. These issues call for improvement in our current therapeutic armamentarium.

Areas covered—In this review, the authors highlight the recent developments in therapies for SLE, and present an overview of drugs which are in early clinical development for SLE. There are many new therapeutic approaches being developed, including those focused on B-cell targets, T-cell downregulation, co-stimulatory blockade, anti-cytokine agents, and kinase inhibition, and Toll-like receptor inhibition. They also discuss peptide therapy as a potential method to re-establish immune tolerance, and some of the challenges ahead in developing and testing novel agents for SLE.

Expert opinion—Many novel agents are currently in development for SLE, but this encouraging news is tempered by several disappointments in clinical trials and provides a timely moment to reflect on the future of therapeutic development in SLE. It seems likely that biological heterogeneity between patients is a major contributor to difficulty in drug design in SLE.

Keywords

systemic lupus erythematosus; cytokine; T cell; B cell

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic relapsing and remitting autoimmune disease (1,2). SLE is characterized by cytokine dysregulation, polyclonal B-cell activation, autoantibody production, and increased immune complex formation due to aberrations

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involving hyperactive B-cells, T-cells, and cells of the monocytic lineage (1,2). Due to earlier diagnosis and better treatment options, the prognosis has markedly improved in the last decades. The 5-year survival of SLE patients has exceeded 90% in most centers. Despite that, there is still a 4.6-fold increased mortality in SLE-affected individuals as compared with the general population (3). The morbidity and mortality related to the disease, especially renal failure and cardiovascular events, are still considered an important issue and there is a large unmet need for therapeutics to effectively control the condition (3). Therefore, it is important to facilitate the development of drugs that have the potential to be more effective and/or less toxic.

Current treatment options include the use of corticosteroids, hydroxychloroquine and other immunosuppressive medications (e.g. azathioprine, mycophenolate, methotrexate, and cyclophosphamide) (4). More recently, belimumab was approved by the FDA for the treatment of SLE (5). In recent years, new treatment strategies have been developed based on the advanced knowledge of the pathogenesis of SLE, in particular treatments have been designed which target specific immune system molecules (2). Given the prominent autoantibody production in SLE, B cells have been a cellular therapeutic target. In addition to autoantibody production, B cells are the key for the activation of the immune system, particularly through cytokines and as antigen-presenting cells. T cells are also critical to the autoimmune response, and B cells are typically activated in a T-cell dependent manner (2). Cytokines are important messenger molecules in the immune system, and modulation of pro-inflammatory cytokines has been attempted in SLE. The paradigm of cytokine blockade has been very successful in other autoimmune and inflammatory conditions such as rheumatoid arthritis and psoriasis. There are a number of anti-cytokine agents in the pipeline for SLE, and the utility of this strategy in SLE has yet to be proven. Endosomal toll-like receptors (TLRs) are expressed on dendritic cells and other innate immune cells, and can be triggered by the immune complexes produced in lupus. This results in inflammatory cytokine production, and there are a number of agents targeting immune complexes, TLRs, and dendritic cells.

Given the heterogeneity and complexity of SLE, the pathway to successful drug development in SLE to date remains uncertain. In fact, a number of phase III trials in SLE have not met their primary endpoint. Despite these issues, a large amount of early stage drug development for SLE is currently taking place. A search of the ClinicalTrials.gov online trial registry for SLE trials returns hundreds of hits; with many drugs in early phase development that collectively target a wide range of different pathways. It seems likely that this continued enthusiasm for drug development in SLE reflects the large unmet therapeutic need. This review will highlight some recent developments in SLE drug development, in particular drugs in early stage of development, and we will discuss the strategies behind the various therapeutic interventions.

2. Conventional SLE therapy

We currently have a limited understanding of the pathogenesis of SLE. This lack of understanding means that we are not able to predict SLE flares or response to treatment, or to quantify the biological heterogeneity of the patient population that contributes to this

heterogeneity in clinical severity and response to treatment. The majority of treatments is still broadly immunosuppressive in action and, hence, carries a significant risk of adverse effects (6,7).

Current SLE treatment includes corticosteroids, anti-malarial agents (mainly hydroxychloroquine), and cytotoxic immunosuppressive agents (7–9). Anti-malarials are one of the main treatments applied in SLE, and are recommended for most patients. Hydroxychloroquine has been shown to decrease the probability of flares, the accrual of damage, and the occurrence of vascular and thrombotic events in SLE patients (10, 11). Hydroxychloroquine has also been shown to facilitate the response to other agents in SLE patients with renal involvement and influence cholesterol levels (10, 11) and has been shown to be effective in the treatment of mucocutaneous and musculoskeletal manifestations as well (6). Corticosteroids are still frequently used to treat SLE, but the biologic effects of corticosteroids are multiple, affecting all tissues, and side-effects are common (8). While corticosteroids may be difficult to replace completely, additional agents that can help to spare the use of corticosteroids would be a significant advance. For moderate to severe disease, immunosuppressants are often used, such as mycophenolate mofetil (MMF), azathioprine (AZT), methotrexate (MTX), cyclophosphamide, and cyclosporine (9).

Although these conventional therapies for SLE can be effective, they are generally immunosuppressive and are not specific to the disease. Many patients with SLE do not respond to first-line treatments, and adverse effects are frequent such as bone loss and weight gain with corticosteroids, gastrointestinal intolerance, and non-specific immunosuppression. Despite the challenges inherent in drug development for SLE, the large unmet clinical need is driving a robust effort to develop new drugs that can impact this difficult condition (12).

3. Recent developments in SLE therapy

A number of therapies targeting various aspects of the immune response are currently in development for SLE. Ideally, these would improve upon the current standard of non-specific immunosuppression and correct some of the specific abnormalities of the innate and adaptive immunological pathways in SLE patients.

3.1 B-cell blockade

Autoreactive B-cells have been frequently implicated in the pathogenesis of SLE as sources of autoantibodies, antigen-presenting cells, and initiators and regulators of inflammation through cytokine secretion (13). B cells seem like a prime target in SLE pathogenesis, and a number of agents targeting this cell type are currently being developed.

3.1.1 Anti-CD20 therapies—SBI-087 is a humanized small modular immunopharmaceutical (SMIP) protein that acts directly against CD20 (3). A Phase I trial in SLE has been completed (NCT00714116), but no results have been published yet (14). Obinutuzumab is a humanized, monoclonal type II CD20 antibody modified by glycoengineering. The glycoengineered Fc portion enhances the binding affinity to the FcγRIII receptor on immune effector cells, resulting in increased antibody-dependent

cellular cytotoxicity, reduced complement-dependent cytotoxicity and enhanced direct non-apoptotic cell death (15). Obinutuzumab has been tested in hematological diseases, but recently a phase II clinical trial for SLE was designed to evaluate the safety and efficacy of Obinutuzumab in participants with lupus nephritis (LN) (NCT02550652) (16).

Previously, Rituximab, a chimeric, murine/human, monoclonal antibody against CD20 demonstrated some evidence for efficacy in the treatment of SLE patients (with or without renal involvement) who were refractory to standard treatment (17–20). Anti-CD20 antibodies result in the depletion and clearance of B cells from the circulation, which presumably could interfere with SLE-related B cell pathology. However, two large multicenter randomized placebo-controlled trials with rituximab in moderately to severely active SLE (EXPLORER) (257 patients) (21) and in proliferative lupus nephritis patients (LUNAR) (144 patients) (22) could not show a significant benefit of rituximab when compared to placebo. Thus, the role for rituximab in the SLE treatment armamentarium remains controversial. However, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have included rituximab as an appropriate off-label treatment for refractory SLE patients with hematological or renal disease (23,24).

The RITUXILUP study provides an alternative approach to the treatment of lupus nephritis (25). An initial report describes an analysis of the first 50 patients, and these data suggest that oral steroid exposure could be safely avoided in the treatment of lupus nephritis using a rituximab-based protocol. A prospective randomized trial is ongoing, recruiting individuals, and this study may support an option that will decrease the long term use of corticosteroids, decreasing steroid-related complications in SLE (26). Another alternate approach to using rituximab includes an upcoming study that will evaluate the sequential use of rituximab and belimumab for the treatment of lupus nephritis (27).

Ocrelizumab, a recombinant humanized monoclonal anti-CD20 antibody has been studied in phase III trials in extrarenal SLE (BEGIN study) (28) and lupus nephritis (BELONG study) (29). However, trials with ocrelizumab were prematurely suspended due to an increased rate of serious infection in the treated group.

3.1.2 Anti-CD22 therapies—CD22 is a B-lymphocyte-restricted type I transmembrane sialoglycoprotein of the Ig superfamily which modulates B-cell function without depleting B-cells (30). Epratuzumab is a fully humanized antibody against CD22 that was tested in 227 patients with moderate to severe SLE disease activity in a 12-week phase IIb randomized study. This study used a novel composite primary endpoint, the BILAG-based Combined Lupus Assessment (BICLA) (31), and included 227 SLE patients with moderate to severe lupus disease activity without active renal or central nervous system involvement (mean BILAG and SLEDAI scores of 15.2 and 14.8, respectively). Treatment with epratuzumab 2400 mg cumulative dose was well tolerated in patients with moderate to severely active SLE, and was associated with improvements in disease activity (3, 31). Two Phase III clinical trials were completed recently; NCT01262365 (EMBODY I) (32) and NCT01261793 (EMBODY II) (33). These trials showed that the safety profile of epratuzumab was similar to earlier studies. Neither study met the primary endpoint (34).

3.1.3 BLyS inhibition—B lymphocyte stimulator (BLyS), also known as B-cell activation factor of the TNF family (BAFF), plays a key role in the survival, activation, and differentiation of B-cells (12). Due to these various roles in the life-cycle and activation of B cells, BLyS has been considered an excellent target for intervention in SLE. High serum levels of BLyS levels and the related B-cell cytokine APRIL (a B-cell proliferation inducing cytokine) have been observed in SLE patients and in murine lupus models (12,35).

Atacicept (also known as TACI-Ig) is a B-cell cytokine blocker. Atacicept is a human fusion protein which functions as a decoy receptor, combining the TACI receptor which binds both BLyS and a related B cell cytokine APRIL with an immunoglobulin Fc domain that assists with maintaining circulating levels of the protein. The receptor can bind both cytokines, but is not associated with any signaling events, and thus is a decoy receptor. Atacicept can affect both B-cells and antibody producing plasma cells, and can cause a decrease IgM and IgG immunoglobulin levels (both protective antibodies and pathogenic autoantibodies). Atacicept was well-tolerated in a phase I trial, which included 48 SLE patients (36). A phase I/II randomized study of atacicept plus mycophenolate mofetil in SLE patients (6 subjects) with nephritis was prematurely terminated due to safety concerns, including an increased number of infections (37). The increased number of infections may be explained by an impact of the drug upon plasma cells that produce protective antibodies, coupled with the immunosuppression related to mycophenlate mofetil. A phase II/III trial of atacicept for SLE (APRIL-SLE) investigated the pharmacodynamics effects in 461 SLE patients and changes in the disease activity biomarkers and protective antibodies (38). No difference was observed between atacicept 75 mg and placebo for flare rate or time to first flare (38). An additional phase IIb trial investigating efficacy of Atacicept in SLE (ADDRESS II) is currently underway.

Tabalumab and blisibimod are also currently being assessed in trials to determine their safety and efficacy in SLE (39). Tabalumab (LY2127399) is a fully human IgG4 monoclonal antibody that inhibits BLyS in both membrane and soluble forms. While tabalumab had biologic activity consistent with BAFF inhibition, as shown by changes in anti-dsDNA, complement, B cell, and immunoglobulins (40), phase III trials of tabalumab (41,42) (NCT01205438 and NCT01488708) did not meet their endpoints and development of tabalumab has been discontinued. Blisibimod (A-623) is a human peptibody immunoglobulin synthetically produced that binds to BLyS and inhibits its interaction with its receptor on B-cells. The efficacy and safety of blisibimod was evaluated in a phase IIb trial (PEARL-SC) which included 547 SLE patients with anti-double stranded DNA or antinuclear antibodies and Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score≥6 (43). Blisibimod was safe and well tolerated at all dose levels with no significant adverse events or infections compared to placebo (43).

Belimumab, a fully human monoclonal antibody that binds to BLyS, is a biological therapy approved for SLE. Belimumab promotes selective B-cell apoptosis (12), and has been shown to ameliorate disease activity in SLE in phase III trials (5,44). It is the first and only biologic agent that has been approved by the FDA for the treatment of SLE, and was the first new drug in almost 50 years to be approved for SLE as an indication (5,44). The trials that

supported FDA approval were large, and demonstrated a statistically significant improvement in constitutional symptoms, musculoskeletal, skin and hematologic manifestations of SLE, however both of these studies excluded SLE patients with active lupus nephritis or neuropsychiatric disease. Thus the wider role of belimumab in SLE management remains unclear. More recently, data suggested that long-term belimumab treatment may protect against organ damage (45). This study (998 SLE patients enrolled) showed that patients with moderate to severe SLE treated with belimumab plus standard of care for 5 years had a lower incidence of organ damage accrual (45).

3.1.4 Plasma cell depletion—Plasma cells are involved in the pathogenesis of SLE. These cells may be classified as long- or short-lived, and relates to whether the cell arises from a germinal center or an extrafollicular locus. In SLE patients, long-lived plasma cells are believed to be responsible for the production of some autoantibodies, such as anti-RNA and anti-cardiolipin antibodies, whereas short-lived plasma cells are the main source of anti-dsDNA antibodies (46). Given the prominent autoantibody response in SLE, plasma cells are a rational target in SLE.

Bortezomib is a nonselective proteasome inhibitor which was developed for multiple myeloma, a cancer of antibody producing plasma cells. The proteasome is important in maintaining an immortal phenotype in the myeloma plasma cells, and seems to play a general role in plasma cell survival. While the exact mechanism is not clear, is seems that proteasome inhibition could promote degradation of anti-apoptotic factors within cells, resulting in increased apoptotic cell death. Bortezomib has been approved for use in multiple myeloma, and the side effect profile includes a risk of peripheral neuropathy (47). A Phase I study of bortezomib in proliferative lupus nephritis was designed, but the study has been withdrawn prior to enrollment (NCT01169857) (48). Two other proteasome inhibitors, delanzomib and carfilzomib, have been tested in mouse lupus and demonstrated some efficacy (47, 49). A selective proteasome inhibitor named ONX0914 was also tested in animal models and showed efficacy (47). There are no clinical trials in human SLE patients yet.

3.2 Peptide therapy

Since T-cells recognize antigens as peptide fragments, synthetic peptides could be created which can mimic and interfere with productive immune responses against specific antigens (8). The exact mechanism by which synthetic peptides induce tolerance is not clear, although generation of regulatory T cells which make suppressive cytokines has been demonstrated in mouse models of lupus (50). While the idea of inducing tolerance to specific antigens instead of broad immunosuppression is attractive, some limitations have to be considered. One major limitation is that the exact autoantigens are not known in SLE, and there is a large diversity among patients with various subtypes of disease and subsets of dominant antigens (51). Therefore, any given peptide may promote tolerance in only a fraction of SLE patients. Stage of disease may also be important, as studies in humans have demonstrated that the autoimmune epitopes targeted evolve to some degree as the disease progresses (52).

Peptides based upon anti-dsDNA antibody sequences (pConsensus) and peptides derived from nucleosomes are currently being tested in pre-clinical disease models (53,54). Rigerimod, also known as P140 peptide, is a 21-mer linear peptide which comes from the small nuclear ribonucleoprotein U1-70K and with a serine phosphorylated in position 140 (55). It was tested in an open-label, dose-escalation phase II study conducted in two centers in Bulgaria. The aim of this trial was to assess the safety, tolerability, and efficacy of the rigerimod peptide in 20 patients with moderately active SLE (55). Rigerimod was shown to be safe and tolerated by these SLE patients. Three subcutaneous administrations of rigerimod at 200 μg significantly ameliorated the clinical and biologic status of SLE patients (55). A phase IIb, double-blind, randomized, placebo-controlled clinical trial of rigerimod was conducted in 204 SLE patients in Europe and Latin America (56). The trial showed that rigerimod 200 μg given three times at 4-week intervals plus standard of care was effective and well tolerated (56). Rigerimod is currently moving into a phase III clinical trial.

Another peptide-based therapy in development is hCDR1, a peptide which has 19 amino acids based on the complementarily determining regions (CDR1) of a human anti-dsDNA antibody. This peptide was tested in a randomized, double-blind, placebo-controlled phase II clinical trial (340 patients enrolled) (PRELUDE) (57). The results were recently published, and while the primary endpoint was not met, some subgroup analyses and secondary endpoints were met (57).

3.3 T-cell target and co-stimulation blockade

The activation of T-cells requires at least two independent signals. First, there is an engagement of the MHC complex and the antigen with the T-cell receptor. Second, co-stimulatory molecules provide the necessary signal for T-cell activation by antigen-presenting cells. The blockade of this co-stimulation mechanism has been effective in murine lupus models (58,59). Co-stimulatory pathways include CD28, CD40/CD40L, cytotoxic T lymphocyte antigen 4 (CTLA4), CD80 (B7-1), and CD86 (B7-2) (60). The CD28:B7 co-stimulatory interaction has been targeted therapeutically in SLE. CD28 is expressed in T-cells, whereas the ligands B7-1 and B7-2 (CD80 and CD86) are found in antigen-presenting cells. CTLA4 inhibits T-cell activation by binding to B7-1 and B7-2 (CD80 and CD86, respectively) expressed on antigen-presenting cells. Therefore, CTLA4 interacts with B7 but inhibits T-cell activation by preventing the co-stimulatory interaction between CD28 and B7 interaction necessary for T-cell activation (13, 61).

Abatacept is a soluble receptor fusion protein which combines CTLA-4 with the Fc portion of IgG1 (62). Abatacept blocks CD80/CD86, thus preventing T-cell co-stimulation via the CD28 pathway. Recently, results of a phase II trial of abatacept in SLE (ACCESS) were published. ACCESS included 134 patients with lupus nephritis and compared intravenous abatacept with cyclophosphamide versus cyclophosphamide only (63). The addition of abatacept to a regimen of cyclophosphamide followed by azathioprine did not improve the outcome of lupus nephritis at either 24 or 52 weeks (63). Previously, a 12-month, randomized, phase II/III, multicenter, international, double-blind trial abatacept which included 298 SLE patients had also not met its primary end point, but suggested some evidence of biological activity and was well tolerated in patients with active class III or IV

lupus nephritis (62). Based upon subset analyses, abatacept will be repeated in SLE patients with nephritis (64) in a phase III study (NCT01714817). RG2077 is another CD80/86–CD28 targeted agent that had been tested in a Phase I/IIa study with patients with lupus nephritis (NCT00094380) (65). No results were released yet. AMG557 is a fully humanized anti-ICOS ligand antibody that was investigated in a phase I, randomized, placebo-controlled, double-blind trial including adult SLE patients (NCT00774943) (66). This co-stimulatory pathway is of interest in SLE, as ICOS-ICOS ligand interactions are important for T cell differentiation and B cell maturation. This study has concluded, but results have not been published (66).

CD40-CD40 ligand (CD40L) is another important co-stimulatory pair that induces T-cell dependent B-cell proliferation and antibody production. Evidence suggests that inhibition of this target with an anti-CD40L antibody may decrease the abnormal immune activation seen in SLE patients (67). Early attempts at interrupting CD40-CD40 ligand interactions in SLE were stopped due to unexpected thrombotic events (67). A new PEGylated anti-CD40L antibody fragment (CDP7657) has recently been shown to be safe and well tolerated in 17 SLE patients in a first-in-human early phase trial (68).

3.3 Cytokine blockade

Cytokines are low-weight soluble proteins produced by different cells in the innate and adaptive immune system. They mediate activation or functional regulation of the immune system (innate and adaptive) by binding to cell surface receptors (62). A number of cytokines are elevated in SLE, and an anti-cytokine could be promising (69). Cytokines such as interferon alpha (IFN-α) and interleukins (IL) 6, 12, and 17 among others have been considered potential targets to reduce chronic inflammation in SLE (70).

3.3.1 Anti–IL-6—Tocilizumab is a humanized monoclonal antibody that inhibits IL-6 signaling, binding directly to the IL-6 receptor and blocking signaling (70). An open-label, dose escalation phase I study of tocilizumab in SLE (16 patients) has been published (71). Although neutropenia may limit the maximum dosage of tocilizumab in SLE patients, the observed clinical and serologic response could warrant further studies to determine efficacy and an optimal dosing regimen (71). Sirukumab is a human, anti-soluble, IL-6, monoclonal antibody which has been developed for use in SLE (72). A Phase I, randomized double-blind, placebo-controlled, dose-ascending study of sirukumab has been completed (73). This study treated 31 cutaneous lupus patients (23 with sirukumab, 8 with placebo) and 15 SLE patients (10 with sirukumab, 5 with placebo) and showed the sirukumab was well tolerated in patients with cutaneous lupus and SLE patients with mild, stable, active disease. A phase II, multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of treatment with Sirukumab in patients with active lupus nephritis (NCT01273389) has finished, but the results are not available yet (74). Most recently, PF-04236921, a fully human monoclonal antibody against to circulating IL-6 had demonstrated positive results. PF-04236921 was tested in a trial which enrolled 183 subjects with active SLE and demonstrated that PF-04236921 neutralizes IL-6 activity, being beneficial in reduce disease manifestations of active SLE (75).

3.3.2 Anti-IL-17A—Secukinumab and ixekizumab are two monoclonal antibodies that inhibit IL-17A. Brodalumab is a monoclonal antibody directed against IL-17 receptor. Increased IL-17A levels have been observed in SLE patients (76,77), and thus IL-17 blockers could be considered as possible therapeutics in SLE. To date, there is no clinical trial ongoing in SLE.

3.3.3 Anti-IL-21—NNC0114-0006 is a humanized, monoclonal antibody against IL-21. The safety and tolerability of NNC0114-0006 in SLE patients were tested in a Phase I trial (NCT01689025) (78). The trial has been terminated, but no results have been released.

3.3.4 Anti-IFN-α—Rontalizumab is a humanized, monoclonal antibody against all IFN-α isoforms (rhuMAb IFN-α) (3). Rontalizumab was tested in a phase II, randomized, double-blind, placebo-controlled trial (238 SLE patients enrolled) that evaluated the efficacy and safety in patients with moderately to severely active SLE (79). In this study, more than 75% of patients demonstrated activation of the IFN pathway in peripheral blood documented by having increased IFN-induced gene transcription. Somewhat surprisingly, this group of high IFN patients did not show a significant response, while in secondary analyses those subjects with low IFN-induced gene expression in peripheral blood cells demonstrated significant responses to treatment (79).

Sifalimumab (MEDI-545) is another monoclonal human antibody that blocks most of IFN-α subtypes impairing signaling through the type I IFN receptor (3). Sifalimumab has been tested in a phase I, multicenter, double-blind, randomized study, which included 161 SLE patients and demonstrated safety and tolerability (80). This combined with the observed clinical activity support the continued clinical development of sifalimumab for SLE (80). A phase II study of sifalimumab in 431 seropositive moderate to severe SLE has been completed (NCT01283139) (81), and the results were presented in fall 2014 in abstract form (81). The phase II study found evidence for efficacy, and adverse events were similar in number between sifalimumab and placebo overall, although a higher rate of herpes zoster was observed in the sifalimumab treated group (81). Interestingly, most of the subjects (over 80%) in this trial had high IFN-induced gene expression in peripheral blood, and the response could be observed in this group when analyzed separately. These data combined with the rontalizumab data suggest that biological diversity between SLE patients with respect to IFN signaling will be important in targeting this pathway, and human studies support a significant amount of variation between patients in IFN pathway activation and regulation (82–84).

Anifrolumab (formerly known as MEDI-546) is a fully human monoclonal antibody that inhibits the type I IFN receptor (IFNAR1), effectively blocking the effects of both IFN-α and IFN-β (85). Anifrolumab suppressed type I IFN-induced gene expression in blood and skin of systemic sclerosis patients in a dose-dependent manner (85). This agent is currently in phase II trials in SLE (86–88). One of these studies showed positive results (89). Anifrolumab significantly reduced disease activity compared with placebo across multiple clinical endpoints (89). While receptor blockade is a more aggressive strategy than just blocking one of the type I IFN cytokines (alpha or beta), the partial responses for each of the anti-IFN-α drugs listed above could suggest that a more aggressive approach may be

beneficial. This would have to be weighed against any potential increase in side-effects resulting from more complete pathway blockade.

Anifrolumab also showed to be effective in blocking IFNAR1 in two open labels phase II Japanese trials (90). However, it is necessary larger double-blind controlled studies to characterize the safety profile adequately and overall safety of anifrolumab (90). More recently, the TULIP (Treatment of Uncontrolled Lupus via the Interferon Pathway) programme was announced which includes two Phase III clinical trials that will evaluate the efficacy and safety of anifrolumab *vs.* placebo in SLE patients. These trials will include patients with moderately to severely active, autoantibody-positive SLE, while receiving conventional SLE therapy (91).

Most recently, an alternative way to block type I IFN has been developed called IFN-α kinoid (IFN-K) (92). Kinoids are composed of inactivated cytokines conjugated to a carrier protein, keyhole limpet hemocyanin (KLH). This protein conjugate is injected as an emulsion with an adjuvant to induce an antibody response against the cytokine, effectively immunizing the person against a naturally occurring cytokine (92). A Phase I/II study was performed to evaluate the safety of IFN-K in 28 women with mild to moderate SLE (92). This study demonstrated that active immunization with IFN-K induced an anti-IFN-α antibody response a polyclonal antibody response, and IFN-induced gene expression was decreased in patients receiving the kinoid (92). IFN-K showed to be well tolerated and immunogenic, although the length of autoantibody response against IFN-α and long-term safety is not currently known. One could imagine that a strong permanent anti-IFN-α antibody response could lead to immunosuppression that could be difficult to reverse.

3.4 Kinase inhibition and other small molecules

Protein kinase inhibitors represent an important emerging class of targeted therapy in SLE. The Janus family kinases (JAKs), Jak1, Jak2, Jak3 and Tyk2, are a subgroup of the non-receptor-type kinases. JAKs are involved in cell growth, survival, development and differentiation of a variety of cells, and are critically important for signaling pathways in the innate and adaptive immune system (93). Tofacitinib is an oral JAK inhibitor that blocks signaling of key cytokines implicated in the pathogenesis of SLE. A phase Ib clinical trial (NCT02535689) is underway, recruiting SLE patients. The aim of this trial is to further evaluate the safety and tolerability of the tofacitinib in SLE patients (94).

Tacrolimus is a calcineurin inhibitor that showed efficacy in SLE patients with nephritis, especially in reducing proteinuria (95). However, its role as a long-term maintenance agent warrants further studies. Tacrolimus has recently been studied in a head-to-head trial of lupus nephritis *vs.* mycophenylate mofetil (150 SLE patients enrolled), and tacrolimus was found to be non-inferior to mycophenylate (96). Sirolimus (Rapamycin) is a related lipophilic macrolide that regulates mitochondrial transmembrane potential and $Ca2^{+}$ fluxing. Rapamycin inhibits IL-2 and other cytokine receptor-dependent signal transduction, via action on mTOR. A prospective study of rapamycin for the treatment of SLE (Rapamune) Phase II (NCT00779194) is ongoing (97).

3.5 TLRs, immune complexes, and dendritic cells

Inhibition of endosomal toll-like receptor (TLR) seems to be an attractive target to control the systemic inflammation in SLE. SLE patients may have an impaired clearance of apoptotic cells, and the antinuclear autoantibodies that characterize SLE can bind with this dead cellular debris, forming nucleic acid-containing immune complexes. Antiviral TLRs can be activated by these self DNA/RNA-containing immune complexes, resulting activation of interferon regulatory factors and the production of type I IFN and other cytokines (98).

RSLV-132 is a mono-specific nuclease Fc-fusion protein that targets and destroys nucleic acid-containing immune complexes, presumably preventing the activation of TLRs in innate immune cells. A double-blind, placebo-controlled dose escalation study of the administration of multiple intravenous doses of RSLV-132 in SLE patients (Phase II) (NCT02194400) is planned, but not recruiting participants yet (99). BIIB059 is a humanized monoclonal antibody that binds to human blood dendritic cell antigen 2 BDCA2 leading to its internalization and the consequent inhibition of TLR-induced type I IFN and other cytokine production by plasmacytoid dendritic cells (pDCs). A single-ascending-dose and multiple-ascending-dose study (Phase I) (NCT02106897) is ongoing, and recruiting participants (100).

IMO-8400, a TLR7/8/9 inhibitor was tested in lupus-prone NZBW/F1 mice. The results were positive and indicated that IMO-8400 suppressed autoimmune antibody production and improved renal function by inhibiting immune responses (101). IMO-8400 is being considered for early stage clinical development. CPG-52364 inhibits signaling following stimulation of TLR7, 8, or 9 in human peripheral blood mononuclear cells (PBMCs). CPG-52364 entered Phase I clinical in healthy subjects development in 2007, however, the results of this trial are unpublished (NCT00547014) (102).

3.6 Drug repurposing

In addition to the new drug development efforts outlined above, there may be agents already approved for use in humans that could be active in SLE. Repurposing existing drugs for SLE would be attractive because some safety data is already available in humans, and the regulatory process would be much less burdensome. One such effort is the Lupus Clinical Investigators Network (LuCIN™) (103). This group used an expert panel to prioritize currently available drugs for potential utility in SLE. The results of this expert panel have been shared, and two of the first lupus drug candidates are a ROCK2 inhibitor and an IL-12/23 inhibitor (103). The group has identified over 60 sites with interest in carrying out repurposing trials, and they plan to incorporate some mechanistic studies along with standard clinical trial outcomes. While some of the drugs listed above are already being repurposed (tacrolimus, JAK inhibitors, etc.), this initiative could allow for some additional existing and approved drugs to be used in SLE management.

4. Conclusion

Advances in the understanding of the immunologic pathways that underlie SLE have opened new opportunities for therapeutic targets. Table 1 summarizes the agents discussed in this

review. There is so much activity in the field it is difficult to be completely comprehensive, but this review covers many of the therapeutic targets that are moving into clinical trials currently. Continued advancements in our knowledge of how to subset patients into biologically important groups according to genetic susceptibility, clinical symptoms, and immunological dysfunction will maximize the therapeutic effect of each agent and minimize its toxicity. This is particularly important for the design of clinical trials, where the correct recruitment and sub-grouping of patients may directly impact the outcome measures. An early example of this is illustrated in the anti-IFN-α trials, in which responding groups differed based upon evidence for activation of this pathway in pre-treatment blood testing. These results are still somewhat paradoxical when the results from the two agents are considered together, and it is clear that we need more detailed information about molecular pathogenesis and disease modeling in humans before we will be able to rationally stratify patients for personalized treatment.

5. Expert Opinion

Many novel agents are currently in development for SLE, but this encouraging news is tempered by several disappointments in large scale clinical trials, and provides a timely moment to reflect on therapeutic development in SLE. There is a large unmet clinical need in SLE at all levels of disease severity, from mild to severe. Existing therapies are characterized by a significant side-effect profile and variable clinical response, and despite these treatments a majority of patients have ongoing disease activity (3,31,38,44). However, designing trials in SLE is challenging due to clinical heterogeneity of patients, short follow up time, outcome measures, and use of concomitant medication, especially corticosteroids, among others. Clinical trials can be designed with strict entry criteria to limit the degree of patient heterogeneity, but SLE trials often recruit slowly even without such strict limitations. Additionally, the results obtained from highly exclusive trials are then not as broadly applicable across diverse clinical scenarios. Thus far trials of agents which have been limited to a specific disease manifestation of SLE, such as nephritis, have been characterized by some successes but also a number of failures, and it seems that stratifying patients by clinical phenotype alone will not answer the dilemma of heterogeneity in SLE.

In addition, it is clear that the molecular characteristics and pathogenic mediators differ between patients, and this could also be an important source of variation in clinical trials. For example, approximately 50% of SLE patients have evidence of high circulating type I IFN activity (82), and background genetic factors contribute to the type I IFN levels in circulation (104), supporting the idea that type I IFN pathway activation is a stable immunogenetic difference between patients. The trials of type I IFN inhibition in SLE summarized above support the idea that this molecular difference between patients will be important to the prediction of therapeutic response, as high vs. low pre-treatment IFN was an important factor in both of the trials that have reported data thus far. This would support the idea that we need to continue to develop a greater knowledge of the immunobiology of SLE in humans to facilitate drug development and implementation of therapeutics in SLE. Pre-clinical work studying lupus patient blood cells will also be critical in early stage development. Also, it will be critical to design assays to detect pathway modulation in

humans due to the therapeutic molecule in early phase trials. This will allow for proof of concept and mechanism, and should also assist with patient selection in later phase studies.

It seems that the Gordian knot in SLE drug development is the unmapped heterogeneity of disease that confounds both clinical and human preclinical studies (how do we study and target the important factors in specific patients when we don't know which ones are important?). In the coming years, increased knowledge of human SLE genetics and immunopathogenesis will provide the sword to cut this knot, informing pre-clinical and clinical studies directed at identifying particular biological subgroups within the SLE population. This will be an iterative process, as the experiences with such targeted trials will provide invaluable experience and information that will guide the next series of trials.

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References

1. Lateef A, Petri M. Biologics in the treatment of systemic lupus erythematosus. Curr Opin Rheumatol. 2010; 22:504–9. [PubMed: 20502332]
2. Merrill JT, Buyon JP, Utset T. A 2014 update on the management of patients with systemic lupus erythematosus. Semin Arthritis Rheum. 2014; 44:e1–2. [PubMed: 25437901]
3*. Fattah Z, Isenberg DA. Recent developments in the treatment of patients with systemic lupus erythematosus: focusing on biologic therapies. Expert Opin Biol Ther. 2014; 14:311–26. This is a nice recent review of biological therapies in SLE. [PubMed: 24387632]
4. Hahn BH. Targeted therapies in systemic lupus erythematosus: successes, failures and future. Ann Rheum Dis. 2011; 70(Suppl 1):i64–i66. [PubMed: 21339222]
5. Wallace DJ, Stoh W, Furie RA, et al. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. Arthritis Rheum. 2009; 61:1168–1178. [PubMed: 19714604]
6. Wofsy D. Recent progress in conventional and biologic therapy for systemic lupus erythematosus. Ann Rheum Dis. 2013; 72(Suppl 2):ii66–8. [PubMed: 23253930]
7. Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med. 2008; 358:929–39. [PubMed: 18305268]
8. Sthoeger Z, Sharabi A, Mozes E. Novel approaches to the development of targeted therapeutic agents for systemic lupus erythematosus. J Autoimmun. 2014; 54:60–71. [PubMed: 24958634]
9. Francis L, Perl A. Pharmacotherapy of systemic lupus erythematosus. Expert Opin Pharmacother. 2009; 10:1481–94. [PubMed: 19505215]
10. Kasitanon N, Fine DM, Haas M, et al. Hydroxychloroquine use predicts complete renal remission within 12 months among patients treated with mycophenolate mofetil therapy for membranous lupus nephritis. Lupus. 2006; 15:366–70. [PubMed: 16830883]
11. Wallace DJ. Antimalarials—the 'real' advance in lupus. Lupus. 2001; 10:385–7. [PubMed: 11434570]
12. Kamal A, Khamashta M. The efficacy of novel B-cell biologics as the future of SLE treatment: a review. Autoimmun Rev. 2014; 13:1094–101. [PubMed: 25149393]
13. Postal M, Costallat LT, Appenzeller S. Biological therapy in systemic lupus erythematosus. Int J Rheumatol. 2012; 2012:578641. [PubMed: 22500177]

14. Study Evaluating The SBI-087 In Subjects With Systemic Lupus Erythematosus (NCT00714116). ClinicalTrials.gov Available at: https://clinicaltrials.gov/ct2/show/NCT00714116?term=NCT00714116&rank=1 [Last accessed 7 April 2015]

15. Illidge T, Klein C, Sehn LH, et al. Obinutuzumab in hematologic malignancies: Lessons learned to date. Cancer Treat Rev. 2015; pii: S0305-7372(15)00148-6. [Epub ahead of print]. doi: 10.1016/j.ctrv.2015.07.003

16. A Study to Evaluate the Safety and Efficacy of Obinutuzumab, an Antibody Targeting Certain Types of Immune Cells, in Participants With Lupus Nephritis (LN) (NCT02550652). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02550652 [Last accessed 8 October 2015]

17. Furtado J, Isenberg DA. B-cell elimination in systemic lupus erythematosus. Clin Immunol. 2013; 146:90–103. [PubMed: 23280492]

18. Duxbury B, Combescure C, Chizzolini C. Rituximab in systemic lupus erythematosus: an updated systematic review and meta-analysis. Lupus. 2013; 22:1489–503. [PubMed: 24135078]

19. Looney RJ, Anolik JH, Campbell D, et al. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. Arthritis Rheum. 2004; 50:2580–9. [PubMed: 15334472]

20. Turner-Stokes T, Lu TY, Ehrenstein MR, et al. The efficacy of repeated treatment with B-cell depletion therapy in systemic lupus erythematosus: an evaluation. Rheumatology (Oxford). 2011; 50:1401–8. [PubMed: 21398661]

21. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus. Arthritis Rheum. 2010; 62:222–233. [PubMed: 20039413]

22. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum. 2012; 64:1215–26. [PubMed: 22231479]

23. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis. 2012; 71:1771–82. [PubMed: 22851469]

24. Aringer M, Burkhardt H, Burmester GR, et al. Current state of evidence on ‘off-label’ therapeutic options for systemic lupus erythematosus, includingbiological immunosuppressive agents, in Germany, Austria and Switzerland-a consensus report. Lupus. 2012; 21:386–401. [PubMed: 22072024]

25**. Condon MB, Ashby D, Pepper RJ, et al. Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. Ann Rheum Dis. 2013; 72:1280–6. Interesting study evaluating the treatment of lupus nephritis with rituximab and mycophenolate mofetil without oral steroids. [PubMed: 23740227]

26. Trial of Rituximab and Mycophenolate Mofetil Without Oral Steroids for Lupus Nephritis (RITUXILUP) (NCT01773616). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01773616?term=NCT01773616&rank=1 [Last accessed 1 February 2016]

27. Rituximab and Belimumab for Lupus Nephritis (NCT02260934). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02260934?term=NCT02260934&rank=1 [Last accessed 1 February 2016]

28. Study to Evaluate Two Doses of Ocrelizumab in Patients With Active Systemic Lupus Erythematosus (BEGIN) (NCT00539838). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT00539838?term=NCT00539838&rank=1 [Last accessed 7 April 2015]

29. A Study to Evaluate Ocrelizumab in Patients With Nephritis Due to Systemic Lupus Erythematosus (BELONG) (NCT00626197). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/study/NCT00626197?term=NCT00626197&rank=1 [Last accessed 7 April 2015]

30. Wallace DJ, Hobbs K, Houssiau F, et al. Randomized controlled trials of epratuzumab (anti-CD-22MAB targeting B cells) reveal clinically meaningful reductions in corticosteroid use with favorable safety profile in moderate and severe flaring SLE patients. Ann Rheum Dis. 2008; 67(Suppl II):212. [PubMed: 17526555]
31. Wallace DJ, Kalunian K, Petri MA, et al. Efficacy and safety of epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, multicentre study. Ann Rheum Dis. 2014; 73:183–90. [PubMed: 23313811]
32. Study of Epratuzumab Versus Placebo in Subjects With Moderate to Severe General Systemic Lupus Erythematosus (EMBODY 1) (NCT01262365). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01262365?term=NCT01262365&rank=1 [Last accessed 7 April 2015]
33. Study of Epratuzumab Versus Placebo in Subjects With Moderate to Severe General Systemic Lupus Erythematosus (SLE) (EMBODY 2) (NCT01261793). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01261793?term=NCT01261793&rank=1 [Last accessed 7 April 2015]
34. Clowse, MEB.; Wallace, DJ.; Furie, R., et al. Efficacy and Safety of Epratuzumab in Patients with Moderate-to-Severe Systemic Lupus Erythematosus: Results from Two Phase 3 Randomized, Placebo-Controlled Trials. ACR Abstract. 2015. http://acrabstracts.org/abstract/efficacy-and-safety-of-epratuzumab-in-patients-with-moderate-to-severe-systemic-lupus-erythematosus-results-from-two-phase-3-randomized-placebo-controlled-trials/
35. Ritterhouse LL, Crowe SR, Niewold TB, et al. B lymphocyte stimulator levels in systemic lupus erythematosus: higher circulating levels in African American patients and increased production after influenza vaccination in patients with low baseline levels. Arthritis Rheum. 2011; 63:3931–41. [PubMed: 22127709]
36. Dall'Era M, Chakravarty E, Wallace D, et al. Reduced B lymphocyte and immunoglobulin levels after atacicept treatment in patients with systemic lupus erythematosus: results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating trial. Arthritis Rheum. 2007; 56:4142–50. [PubMed: 18050206]
37. Ginzler EM, Wax S, Rajeswaran A, et al. Atacicept in combination with MMF and corticosteroids in lupus nephritis: results of a prematurely terminated trial. Arthritis Res Ther. 2012; 14:R33. [PubMed: 22325903]
38. Isenberg D, Gordon C, Licu D, et al. Efficacy and safety of atacicept for prevention of flares in patients with moderate-to-severe systemic lupus erythematosus (SLE): 52-week data (APRIL-SLE randomised trial). Ann Rheum Dis. 2014 Jun 20. pii: annrheumdis-2013-205067.
39. Selmi C, Generali E, Massarotti M, et al. New treatments for inflammatory rheumatic disease. Immunol Res. 2014; 60:277–88. [PubMed: 25381481]
40. Isenberg, D.; Merrill, J.; Hoffman, R., et al. OP0184 efficacy and safety of tabalumab in patients with systemic lupus erythematosus (SLE): results from 2 phase 3, 52-week, multicenter, randomized, placebo-controlled trials. EULAR Abstract. 2015. http://ard.bmj.com/content/74/Suppl_2/141.1
41. A Study of LY2127399 in Patients With Systemic Lupus Erythematosus (NCT01205438). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01205438?term=NCT01205438&rank=1 [Last accessed 8 April 2015]
42. An Open-Label Study in Participants With Systemic Lupus Erythematosus (Illuminate-X) (NCT01488708). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01488708?term=NCT01205438&rank=2 [Last accessed 8 April 2015]
43. Furie RA, Leon G, Thomas M, et al. A phase 2, randomised, placebo-controlled clinical trial of blisibimod, an inhibitor of B-cell activating factor, in patients with moderate-to-severe systemic lupus erythematosus, the PEARL-SC study. Ann Rheum Dis. 2015; 74:1667–75. [PubMed: 24748629]
44. Manzi S, Sánchez-Guerrero J, Merrill JT, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Ann Rheum Dis. 2012; 71:1833–8. [PubMed: 22550315]

45**. Bruce, IN.; Urowitz, M.; van Vollenhoven, R., et al. 5-year organ damage accrual and safety in patients with SLE treated with belimumab plus standard of care. EULAR Abstract. 2015. http://www.abstracts2view.com/eular/view.php?nu=EULAR15L_OP0186. This abstract suggests some novel long-term benefit of belimumab treatment

46*. Liu Z, Zou Y, Davidson A. Plasma cells in systemic lupus erythematosus: the long and short of it all. Eur J Immunol. 2011; 41:588–91. This is a nice review of plasma cells in SLE. [PubMed: 21341259]

47. Ichikawa HT, Conley T, Muchamuel T, et al. Beneficial effect of novel proteasome inhibitors in murine lupus via dual inhibition of type I interferon and autoantibody-secreting cells. Arthritis Rheum. 2012; 64:493–503. [PubMed: 21905015]

48. Velcade for Proliferative Lupus Nephritis (NCT01169857). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01169857?term=NCT01169857&rank=1 [Last accessed 8 April 2015]

49. Seavey MM, Lu LD, Stump KL, et al. Novel, orally active, proteasome inhibitor, delanzomib (CEP-18770), ameliorates disease symptoms and glomerulonephritis in two preclinical mouse models of SLE. Int Immunopharmacol. 2012; 12:257–270. [PubMed: 22178195]

50. Kang HK, Liu M, Datta SK. Low-dose peptide tolerance therapy of lupus generates plasmacytoid dendritic cells that cause expansion of autoantigen-specific regulatory T cells and contraction of inflammatory Th17 cells. J Immunol. 2007; 178:7849–58. [PubMed: 17548623]

51. Amarilyo G, Hahn B, La Cava A. Preclinical studies with synthetic peptides in systemic lupus erythematosus. Front Biosci (Landmark Ed). 2012; 17:1940–7. [PubMed: 22201847]

52. Arbuckle MR, McClain MT, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med. 2003; 349:1526–33. [PubMed: 14561795]

53. Skaggs BJ, Lourenço EV, Hahn BH. Oral administration of different forms of a tolerogenic peptide to define the preparations and doses that delay anti-DNA antibody production and nephritis and prolong survival in SLE-prone mice. Lupus. 2011; 20:912–20. [PubMed: 21562020]

54. Zhang L, Bertucci AM, Ramsey-Goldman R, et al. Major pathogenic steps in human lupus can be effectively suppressed by nucleosomal histone peptide epitope-induced regulatory immunity. Clin Immunol. 2013; 149:365e78. [PubMed: 24211843]

55. Muller S, Monneaux F, Schall N, et al. Spliceosomal peptide P140 for immunotherapy of systemic lupus erythematosus: results of an early phase II clinical trial. Arthritis Rheum. 2008; 58:3873–83. [PubMed: 19035498]

56. Zimmer R, Scherbarth HR, Rillo OL, et al. Lupuzor/P140 peptide in patients with systemic lupus erythematosus: a randomised, double-blind, placebo-controlled phase IIb clinical trial. Ann Rheum Dis. 2013; 72:1830–5. [PubMed: 23172751]

57. Urowitz MB, Isenberg DA, Wallace DJ. Safety and efficacy of hCDR1 (Edratide) in patients with active systemic lupus erythematosus: results of phase II study. Lupus Sci Med. 2015; 2:e000104. [PubMed: 26301100]

58. Schiffer L, Sinha J, Wang X, et al. Short term administration of costimulatory blockade and cyclophosphamide induces remission of systemic lupus erythematosus nephritis in NZB/W F1 mice by a mechanism downstream of renal immune complex deposition. J Immunol. 2003; 171:489–497. [PubMed: 12817034]

59. Navarra SV. Immune therapy of lupus: what is on the horizon? Nephrol Dial Transplant. 2006; 21:579–81. [PubMed: 16384833]

60. Xiong W, Lahita RG. Novel treatments for systemic lupus erythematosus. Ther Adv Musculoskeletal Dis. 2011; 3:255–66.

61. Haubitz M. New and emerging treatment approaches to lupus. Biologics. 2010; 4:263–71. [PubMed: 20859453]

62. Furie R, Nicholls K, Cheng TT, et al. Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. Arthritis Rheumatol. 2014; 66:379–89. [PubMed: 24504810]

63. ACCESS Trial Group. Treatment of lupus nephritis with abatacept: the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study. Arthritis Rheumatol. 2014; 66:3096–104. [PubMed: 25403681]
64. Efficacy and Safety Study of Abatacept to Treat Lupus Nephritis (NCT01714817). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/study/NCT01714817?term=Abatacept&rank=46 [Last accessed 15 September 2015]
65. Treating Systemic Lupus Erythematosus (SLE) Patients With CTLA4-IgG4m (RG2077) (NCT00094380). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT00094380?term=NCT00094380&rank=1 [Last accessed 8 October 2015]
66. A Study of AMG 557 in Adults With Systemic Lupus Erythematosus (NCT00774943). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT00774943?term=NCT00774943&rank=1 [Last accessed 8 April 2015]
67. Boumpas DT, Furie R, Manzi S, et al. A short course of BG9588 (anti-CD40 ligand antibody) improves serologic activity and decreases hematuria in patients with proliferative lupus glomerulonephritis. Arthritis Rheum. 2003; 48:719–27. [PubMed: 12632425]
68. Tocoian A, Buchan P, Kirby H, et al. First-in-human trial of the safety, pharmacokinetics and immunogenicity of a PEGylated anti-CD40L antibody fragment (CDP7657) in healthy individuals and patients with systemic lupus erythematosus. Lupus. 2015; 24:1045–56. [PubMed: 25784719]
69. Postal M, Appenzeller S. The role of Tumor Necrosis Factor-alpha (TNF-α) in the pathogenesis of systemic lupus erythematosus. Cytokine. 2011; 56:537–43. [PubMed: 21907587]
70. La Cava A. Anticytokine therapies in systemic lupus erythematosus. Immunotherapy. 2010; 2:575–82. [PubMed: 20636010]
71. Illei GG, Shirota Y, Yarboro CH, et al. Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. Arthritis Rheum. 2010; 62:542–52. [PubMed: 20112381]
72. Thanarajasingam U, Niewold TB. Sirukumab: a novel therapy for lupus nephritis? Expert Opin Investig Drugs. 2014; 23:1449–55.
73. Szepietowski JC, Nilganuwong S, Wozniacka A, et al. Phase I, randomized, double-blind, placebo-controlled, multiple intravenous, dose-ascending study of sirukumab in cutaneous or systemic lupus erythematosus. Arthritis Rheum. 2013; 65:2661–71. [PubMed: 23896980]
74. An Efficacy and Safety Study of CNTO 136 in Patients With Active Lupus Nephritis (NCT01273389). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01273389?term=NCT01273389&rank=1 [Last accessed 8 April 2015]
75. Smolen, J.; Popa, S.; Szombati, I., et al. OP0185 Significant Clinical Improvement and Reduction of Severe Flares Following Administration of an IL-6 Monoclonal Antibody in Systemic Lupus Erythematosus (SLE) Subjects with High Disease Activity. EULAR Abstract. 2015. http://ard.bmj.com/content/74/Suppl_2/141.2.abstract
76*. Comte D, Karampetsou MP, Tsokos GC. T cells as a therapeutic target in SLE. Lupus. 2015; 24:351–63. A comprehensive review of the roles T cells play in lupus and their potential as a therapeutic target. [PubMed: 25801878]
77. Patel DD, Lee DM, Kolbinger F, et al. Effect of IL-17A blockade with secukinumab in autoimmune diseases. Ann Rheum Dis. 2013; 72(Suppl2):ii116–23. [PubMed: 23253932]
78. An Investigation of Safety and Tolerability of NNC0114-0006 in Subjects With Systemic Lupus Erythematosus (SLE) (NCT01689025). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01689025?term=NCT01689025&rank=1 [Last accessed 8 October 2015]
79. Kalunian KC, Merrill JT, Maciuca R, et al. A Phase II study of the efficacy and safety of rontalizumab (rhuMAb interferon-α) in patients with systemic lupus erythematosus (ROSE). Ann Rheum Dis. 2015 Jun 2. pii: annrheumdis-2014-206090.
80. Petri M, Wallace DJ, Spindler A, et al. Sifalimumab, a human anti-interferon-α monoclonal antibody, in systemic lupus erythematosus: a phase I randomized, controlled, dose-escalation study. Arthritis Rheum. 2013; 65:1011–21. [PubMed: 23400715]
81. Khamashta, M.; Merrill, JT.; Werth, VP., et al. Safety and Efficacy of Sifalimumab, an Anti IFN-Alpha Monoclonal Antibody, in a Phase 2b Study of Moderate to Severe Systemic Lupus

Erythematosus (SLE). ACR Annual Meeting Late-Breaking Abstract. 2014. http://acrabstracts.org/abstracts/safety-and-efficacy-of-sifalimumab-an-anti-ifn-alpha-monoclonal-antibody-in-a-phase-2b-study-of-moderate-to-severe-systemic-lupus-erythematosus-sle/

82. Weckerle CE, Franek BS, Kelly JA, et al. Network analysis of associations between serum interferon-α activity, autoantibodies, and clinical features in systemic lupus erythematosus. Arthritis Rheum. 2011; 63:1044–53. [PubMed: 21162028]
83. Ko K, Koldobskaya Y, Rosenzweig E, et al. Activation of the Interferon Pathway is Dependent Upon Autoantibodies in African-American SLE Patients, but Not in European-American SLE Patients. Front Immunol. 2013; 4:309. [PubMed: 24101921]
84*. Sharma S, Jin Z, Rosenzweig E, et al. Widely divergent transcriptional patterns between SLE patients of different ancestral backgrounds in sorted immune cell populations. J Autoimmun. 2015; 60:51–8. Recent study which demonstrates biological differences between patients of different ancestral backgrounds and also between different patients of the same ancestral background. [PubMed: 25921064]
85. Wang B, Higgs BW, Chang L, et al. Pharmacogenomics and translational simulations to bridge indications for an anti-interferon-α receptor antibody. Clin Pharmacol Ther. 2013; 93:483–92. [PubMed: 23511714]
86. Safety and Tolerability of Intravenous Dose of MEDI-546 in Japanese Subjects With Systemic Lupus Erythematosus (NCT01559090). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01559090?term=MEDI-546&rank=2 [Last accessed 8 April 2015]
87. A Study of the Efficacy and Safety of MEDI-546 in Systemic Lupus Erythematosus (NCT01438489). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01438489?term=MEDI-546&rank=3 [Last accessed 8 April 2015]
88. An Open-label Study to Evaluate the Long-term Safety of MEDI-546, for the Treatment of Systemic Lupus Erythematosus, in Adults (NCT01753193). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01753193?term=MEDI-546&rank=4 [Last accessed 8 April 2015]
89. Furie, R.; Merrill, JT.; Werth, VP., et al. Anifrolumab, an Anti-Interferon Alpha Receptor Monoclonal Antibody, in Moderate to Severe Systemic Lupus Erythematosus (SLE). ACR Abstract. 2015. http://acrabstracts.org/abstract/anifrolumab-an-anti-interferon-alpha-receptor-monoclonal-antibody-in-moderate-to-severe-systemic-lupus-erythematosus-sle/
90. Chang, L.; Wang, L.; Brohawn, P., et al. Target Modulation of a Type I Interferon (IFN) Gene Signature with Sifalimumab or Anifrolumab in Systemic Lupus Erythematosus (SLE) Patients in Two Open Label Phase 2 Japanese Trials. ACR Abstract. 2014. http://acrabstracts.org/abstracts/target-modulation-of-a-type-i-interferon-ifn-gene-signature-with-sifalimumab-or-anifrolumab-in-systemic-lupus-erythematosus-sle-patients-in-two-open-label-phase-2-japanese-trials/
91. https://www.astrazeneca.com/our-company/media-centre/press-releases/2015/AstraZeneca-presents-positive-new-data-on-anifrolumab-in-lupus-at-American-College-of-Rheumatology-Annual-Scientific-Meeting-10112015.html
92. Lauwerys BR, Hachulla E, Spertini F, et al. Down-regulation of interferon signature in systemic lupus erythematosus patients by active immunization with interferon α-kinoid. Arthritis Rheum. 2013; 65:447–56. [PubMed: 23203821]
93. Yildirim-Toruner C, Diamond B. Current and novel therapeutics in the treatment of systemic lupus erythematosus. J Allergy Clin Immunol. 2011; 127:303–12. quiz 313–4. [PubMed: 21281862]
94. Safety of Tofacitinib, an Oral Janus Kinase Inhibitor, in Systemic Lupus Erythematosus (NCT02535689). linicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02535689?term=Tofacitinib&rank=5 [Last accessed 5 October 2015]
95. Yap DY, Ma MK, Mok MM, et al. Long-term data on tacrolimus treatment in lupus nephritis. Rheumatology (Oxford). 2014; 53:2232–7. [PubMed: 24996908]
96. Mok CC, Ying KY, Yim CW, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. Ann Rheum Dis. 2016; 75:30–6. [PubMed: 25550339]

97. Prospective Study of Rapamycin for the Treatment of SLE (Rapamune) (NCT00779194). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT00779194?term=NCT00779194&rank=1 [Last accessed 5 October 2015]

98. Jensen MA, Niewold TB. Interferon regulatory factors: critical mediators of human lupus. Transl Res. 2015; 165:283–95. [PubMed: 25445206]

99. RSLV-132 Biologic Proof-of-Concept in Systemic Lupus Erythematosus (NCT02194400). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02194400?term=RSLV-132&rank=1 [Last accessed 15 September 2015]

100. Study Evaluating the Safety Tolerability Pharmacokinetics of Single Doses multiple Doses of BIIB 059 in Healthy Volunteers and Participants With Systemic Lupus Erythematosus (NCT02106897). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02106897 [Last accessed 15 September 2015]

101. Li J, Wang X, Zhang F, et al. Toll-like receptors as therapeutic targets for autoimmune connective tissue diseases. Pharmacol Ther. 2013; 138:441–51. [PubMed: 23531543]

102. First Safety Study in Humans of a Single Dose of CPG 52364 (NCT00547014). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT00547014?term=CpG-52364&rank=1 [Last accessed 5 October 2015]

103. Lupus Clinical Investigators Network (LuCIN™). Available at: http://www.ampelbiosolutions.com/lrxl-stat [Last accessed 5 October 2015]

104. Ghodke-Puranik Y, Niewold TB. Immunogenetics of systemic lupus erythematosus: A comprehensive review. J Autoimmun. 2015; 64:125–36. [PubMed: 26324017]

Highlights

- Despite conventional therapies for SLE, many patients have ongoing disease activity.
- Many novel agents are currently in development for SLE.
- Advances in the understanding of the immunologic pathways that underlie SLE have opened new opportunities for therapeutic targets.
- Biological therapy has shown efficacy and safety, and is promising in SLE.
- Biological heterogeneity between patients likely represents a major limitation to previous clinical trials in SLE.

Table 1

Summary of new therapies being developed for SLE treatment

TARGET	DRUG	CLINICAL TRIAL	
		PHASE	MAIN RESULTS
B-cell target			
CD20	SBI-087 (14)	I	No results released
	Obinutuzumab (15)	II	Ongoing
	Rituximab (21, 22, 25, 26, 27)	II/III	No benefit in proliferative lupus nephritis
		II	Ongoing
		III	RITUXILUP study demonstrates that oral steroid exposure can be safely avoided in the treatment of lupus nephritis
	Ocrelizumab (28,29)	III	No benefit in lupus nephritis. Prematurely suspended, due to an increased rate of serious infection
CD22	Epratuzumab (31–33)	IIb	Well-tolerated in patients with moderately to severely active SLE. Improvement of disease activity
		III	Neither study met the primary endpoint.
BlyS	Atacicept (37,38)	II	Ongoing
	Tabalumab (40–42)	III	Development discontinued
	Blisibimod (43)	IIb	Safe and well-tolerated, no significant increase in adverse events
	Belimumab (5)	III	Reduction in disease activity and new flares, FDA approved
Plasma cell depletion	Bortezomib (48)	I	Withdrawn prior to enrollment
	Delanzomib (47,49)	—	No clinical trials in human SLE patients
	Carfilzomib (47,49)	—	No clinical trials in human SLE patients
	ONX0914 (47)	—	No clinical trials in human SLE patients
Peptides			
T-cell	pConsensus (53)	—	Early-phase studies
T-cell	Anti-nucleosome (54)	—	Early-phase studies
T-cell	Rigerimod (P140) (55,56)	II	Three subcutaneous administrations of P140 at 200 μg significantly ameliorated the clinical and biologic status of SLE patients
B-cell	Edratide (hCDR1) (57)	II	Primary endpoint not met, pre-specified secondary endpoint and subset effects observed
T-cell target and costimulatory blockers			
CD80/CD86	Abatacept (62–64)	II	Addition to cyclophosphamide did not improve the outcome of lupus nephritis at either 24 or 52 weeks
B7RP1	AMG557 (66)	I	No results released
CD40L	CDP7657 (PEGylated anti-CD40L) (68)	I	Single doses showed acceptable pharmacokinetics and safety and tolerability in SLE patients
Cytokine Blockers			
Anti-IL-6 receptor	Tocilizumab (71)	I	Neutropenia limited the maximum dosage of tocilizumab in SLE patients, but clinical and serologic responses were promising

TARGET	DRUG	CLINICAL TRIAL	
		PHASE	MAIN RESULTS
Anti-IL-6	Sirukumab (73,74)	I	Well tolerated in patients with cutaneous lupus and SLE patients with mild, stable, active disease
		II	No results released
	PF-04236921 (75)	II	Severe flare reduction
Anti-IL17A	Secukimumab	—	N/A
	Ixekizumab	—	N/A
	Brodalumab	—	N/A
Anti-IL21	NNC0114-0006 (78)	I	No results released
Anti-IFN-α/Anti-IFNR	Sifalimumab (MEDI-545) (80,81)	I	Good safety and tolerability
		II	Efficacy and safety promising in SLE, worked in high IFN subjects when analyzed separately
	Rontalizumab (79)	II	Not effective in high IFN SLE patients, improved disease activity and flares in low IFN patients
	Anifrolumab (MEDI-546) (86–90)	II	Ongoing
		II	Effective in blocking IFNAR1
	IFN-K (IFN-α Kinoid) (92)	I/II	IFN-K activity correlated with baseline expression of IFN-induced genes
Kinase inhibition and small molecules			
JAK inhibitor	Tofacitinib (94)	Ib	Ongoing
Calcineurin inhibitor	Tacrolimus (95,96)	I//II	Ongoing
mTOR	Sirolimus (Rapamycin) (97)	II	Ongoing
Other targets			
Anti-immune-complex	RSVL-132 (99)	II	Ongoing
Anti-dendritic cell	BIIB059 (100)	I	Ongoing
TLR7/TLR8/TLR9 inhibitor	CPG-52364 (102)	I	No results released
	IMO-8400 (101)	—	No clinical trials in human SLE patients