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Current and Novel Therapeutics in Treatment of SLE

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Abstract

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with significant clinical heterogeneity. Recent advances in our understanding of the genetic, molecular and cellular basis of autoimmune diseases and especially SLE have led to the application of novel and targeted treatments. While many treatment modalities are effective in lupus-prone mice, the situation is more complex in humans. This article reviews the general approach to the therapy of SLE, focusing on current approved therapies and novel approaches that might be used in the future.

Keywords

SLE; treatment

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with heterogeneous clinical manifestations and disease course. It is characterized by the dysregulated innate and adaptive immune pathways and the development of anti-nuclear antibodies. The current treatment approach includes antimalarials, steroidal and non-steroidal anti-inflammatory agents and immunosuppressive drugs, including cyclophosphamide, azathioprine, mycophenolic acid and methotrexate. Although there is a dramatic improvement in the prognosis for SLE patients, treatment of those with active disease refractory to traditional therapies continues to be a real challenge. On the horizon are new targeted therapies specifically designed to block pathways involved in disease pathogenesis. As we understand the initiation and progression of the disease better, we can consider therapeutic options that focus on blocking defined phases of disease pathogenesis.

In this article, we will review information on the general approach to the therapy of SLE, focusing on current approved therapies and novel approaches that might be used in the future.

SYSTEMIC INFLAMMATION DIRECTED TREATMENT

1. Antimalarials-Hydroxychloroquine

Antimalarials remain as first line treatment for patients with mild SLE along with nonsteroidal anti-inflammatory drugs. Hydroxychloroquine is effective in the treatment of mild SLE manifestations as well as in preventing the occurrence of new mild SLE manifestations, but it is ineffective in preventing the occurrence of severe SLE manifestations.[1,2] Antimalarials inhibit phagosome function, thereby inhibiting TLR activation leading to a down-regulation of IFN-α and decreasing the antigen processing necessary for autoantigen presentation. Hydroxychloroquine also has a beneficial effect on dyslipidemia.[3] Although some still recommend discontinuing it during pregnancy, there is evidence supporting its safety.[4]

2. Corticosteroids

Glucocorticoids are the mainstay of treatment in SLE, especially at the beginning of a flare. They have strong anti-inflammatory effects on both acquired and innate immune pathways. They inhibit B and T cell responses and effector functions of monocytes and neutrophils through inhibition of NF-κB activity.[5] In lupus, glucocorticoids are typically neutrophils administered orally on a daily basis. When doses greater than 60 mg per day are required, patients may receive intravenous methylprednisolone pulse therapy (30 mg /kg, maximum 1 g /day) although such treatment has not been shown to be more effective than doses of 100 to 200 mg daily and may increase toxicity. Recently, it was demonstrated, in vitro and in vivo, that stimulation of plasmacytoid dendritic cells (pDCs) through TLR7 and 9 can account for a reduced activity of glucocorticoids to inhibit the IFN pathway in SLE patients and in two lupus-prone mouse strains. It is, therefore, possible that inhibitors of TLR7 and 9 signaling could be effective corticosteroid-sparing drugs.[6]

3. Cyclophosphamide

Pulse cyclophosphamide (CTX) defined the standard of care for lupus nephritis for many years and is usually used in conjunction with corticosteroids. The optimal dosing regimen had not been determined. The side effects of this agent are infertility, malignancy, hemorrhagic cystitis and infection.

The comparison of “mini-pulse” CTX with conventional pulse CTX therapy (National Institutes of Health (NIH) trials) showed no difference in efficacy between the groups, as defined by frequency of renal deterioration or death, mean serum creatinine, amount of proteinuria, or overall lupus damage score after 10 years of follow-up[7]. Other immunosuppressive agents are preferred for maintaining remission, such as azathioprine and mycophenolate mofetil, because of their greater safety. CTX is also used with corticosteroids in patients with severe neuropsychiatric involvement.

4. Mycophenolate mofetil

This immunosuppressive drug has been used for several years in human organ transplantation. Mycophenolate mofetil (MMF) is the prodrug of mycophenolic acid, an inhibitor of inosine monophosphate dehydrogenase. This enzyme controls the de novo synthesis of guanosine nucleotides, a step essential for DNA synthesis in lymphocytes. The active metabolite is an inhibitor of purine synthesis and blocks the proliferation of activated T and B lymphocytes.

It has been compared to CTX in a number of case series for the treatment of lupus nephritis. In an open label study comparing MMF and pulse CTX as induction therapy for lupus nephritis, MMF was found to be more efficacious than CTX[8]. The main side effects of

MMF were gastrointestinal events such as diarrhea, nausea and vomiting, minor infectious episodes, and rare cases of leucopenia. In another study, MMF was as effective as pulse CTX in maintaining renal response and caused fewer serious adverse events[9]. Results of a large multinational trial examining the efficacy of MMF compared to intravenous CTX over 6 months as induction and either MMF or azathioprine (AZA) as maintenance therapy in lupus nephritis for 36 months show comparable results in the MMF and CTX groups. Moreover, no safety advantage was shown for MMF during the induction phase. In contrast, the maintenance phase demonstrated a clear advantage of MMF over AZA.

5. Azathioprine

AZA, a purine analogue, has a major role in the treatment of SLE, especially as a corticosteroid-sparing agent. AZA is inactive until it is metabolized to mercaptopurine by the liver and erythrocytes at which point it inhibits DNA synthesis and so prevents cell proliferation in the immune system. Toxicity to the GI tract, oral ulcers, nausea, vomiting, diarrhea, epigastric pain, is common. Dose-related toxicity to the bone marrow results in leucopenia and less commonly, thrombocytopenia and anemia. While it has superior efficacy to corticosteroids in the treatment of diffuse proliferative lupus nephritis, it is less effective than CTX.

5. Methotrexate (MTX)

Methotrexate is a folic acid analogue and a potent competitive inhibitor of dihydrofolate reductase (DHFR), and acts by inhibition of both DNA and RNA synthesis. MTX has a role in the management of resistant arthritis and skin disease in SLE as a steroid-sparing agent. It does not have a role in the treatment of SLE patients with major organ involvement[10].

IMMUNE CELL TARGETED THERAPIES

B cells are at the center of SLE pathogenesis. In addition to secretion of autoantibodies, B cells can take up autoantigens, through cell- surface immunoglobulin (the B cell receptor (BCR)) and present them to T cells, as well as regulate and organize inflammatory responses through cytokine secretion and regulation of other immune cells. Ideally, B cell targeted therapies would eliminate pathogenic B cells or promote the expansion and function of protective B cells, or both. Current therapies that target the B-cell compartment include antibodies to B-cell surface antigens, tolerogens, blocking of co-stimulatory molecules, and inhibition of cytokines with direct B-cell effects. B cells have multiple pathogenic roles. B cells secrete autoantibodies. They can also take up autoantigens and present them to T cells in addition to regulating and organizing inflammatory responses through cytokine secretion and regulation of other immune cells. Agents that target B cells are the monoclonal antibodies rituximab, ofatumumab, ocrelizumab and veltuzumumab (anti-CD20), epratuzumab (anti-CD22), belimumab (anti-BAFF) and atacicept (anti-BAFF and APRIL).

Anti-CD20 (Rituximab) is a chimeric mouse/human monoclonal antibody against the B-cell-specific antigen CD20.[11] It was approved by FDA for the treatment of relapsed or refractory B-cell lymphoma in 1997.[12] There are data on the efficacy of rituximab in a variety of other autoimmune diseases, including rheumatoid arthritis (RA), multiple sclerosis (MS), type I diabetes, ANCA-positive vasculitis, IgM-antibody-associated polyneuropathy, idiopathic thrombocytopenic purpura (ITP), and autoimmune hemolytic anemia. In mice, Rituximab targets B lymphocytes in vivo from the pre-B stage in the bone marrow when CD20 is first expressed to the mature naïve and memory B-cell stages. In humans, it clearly depletes B cells from peripheral blood, but the degree of tissue depletion is not precisely known. CD20 is not found on pro-B cells, pre-B cells or mature plasma cells. Because rituximab does not eliminate plasma cells, it does not markedly reduce

immunoglobulin levels. Because there is sparing of T cells, rituximab is less immunosuppressive than other cytolytic therapies.

Retrospective analyses and open label Phase I/II trials of rituximab were promising in both childhood-onset and adult-onset active and refractory SLE.[13,14] Case series with severe refractory SLE (n=7) suggested that re-treatment with rituximab is safe and clinical response is sustained up to 12 months on average.[13] Rituximab also showed promising efficacy in refractory neuropsychiatric manifestations of SLE. Unfortunately, the placebo-controlled Phase II/III EXPLORER and LUNAR trials of rituximab in SLE failed to meet the primary and secondary endpoints.[15,16]

Other antiCD-20 monoclonal antibodies are atumumab, ocrelizumab and veltuzumumab. A Phase III study using ocrelizumab (in addition to prednisolone, low-dose cyclophosphamide and MMF or azathioprine) in lupus nephritis was terminated due to infectious complications.

Anti- CD22 (Epratuzumab)

Epratuzumab is a monoclonal antibody against CD22, a B cell-specific surface antigen involved in the modulation of BCR signaling.[17] It causes a modest 35–45% decrease in B cells, but no change in immunoglobulin levels. UCB and Immunomedics announced positive results in a Phase IIb trial for SLE. The trial enrolled 227 patients, 70% with “severely active disease”. At week 12, there was a 25% difference between the epratuzumab and the placebo-treated patients. A “combined index endpoint” was used as the primary outcome measure. The details of this index were not released but it primarily measured BILAG improvement. At this time, there is inadequate information to evaluate the study.[18,19]

Abetimus (LJP-394)

Abetimus (LJP-394) is a B cell tolerogen. B cell tolerogens are molecules that bind to and extensively crosslink membrane immunoglobulin, thereby causing either anergy (functional inactivation) or deletion of B cells expressing an antigen reactive BCR. LPJ-394 was the first B-cell tolerogen developed for SLE and was studied in human trials for the treatment of non-renal lupus and lupus nephritis. It contains four strands of double-stranded (ds) DNA bound to a carrier and binds strongly to anti-dsDNA antibodies. Initial trials suggested a reduction in renal flares in patients who have high affinity antibodies to the DNA epitope contained within abetimus molecule. However, other trials failed to show any difference between treated and untreated groups in treatment of renal flare, or in time to initiation of further therapy. Similarly, there was no difference in major nonrenal flares.[20] After an analysis of a Phase III ASPEN trial, the trial was terminated when interim efficacy analysis indicated it would be futile to continue study.[21,22]

Belimumab is a fully human monoclonal antibody that binds to and inhibits action of the soluble form of B lymphocyte stimulator (BLyS) (also known as BAFF-B-cell lymphocyte activating factor). When belimumab is bound to soluble form of BLyS, it prevents BLyS from binding to receptors TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor), BCMA (B-cell maturation antigen), and BAFF-R (B-cell lymphocyte activating factor receptor). BAFF levels are elevated in many SLE patients and in some studies correlate with disease activity. Belimumab was efficacious in a large Phase II, dose-escalating, double-blind, placebo-controlled trial.[23] Although the trial did not meet the endpoint of improvement in SELENA-SLEDAI disease activity score at week 52, clinical data from the Phase II trial were used to develop a SRI (SLE response index). Two large Phase III studies BLISS-52 and BLISS-76, demonstrated significant clinical efficacy of Belimumab, although benefit was not sustained at week 76.[23,24] Biological activity of

Belimumab was also demonstrated; the total number of B cells, naïve B cells, plasmablasts, IgG, IgA, IgM and IgG anti-dsDNA titers decreased in the Belimumab- treated group.[24]

Overall, belimumab has been relatively well tolerated with discontinuation rates and adverse events similar to those of placebo. Approval of belimumab for the treatment of autoantibody-positive patients with active SLE was recommended by the US Food and Drug Administration (FDA) Arthritis Advisory Committee on November 16, 2010. If belimumab is approved by the FDA, its US market launch would be expected in 2011. B cell depletion causes markedly increased serum levels of BAFF. Increased in BAFF leads to macrophage activation and promotes survival of autoreactive B cells. Combining BAFF inhibition and B cell depletion may have a synergistic effect and prevent a reconstitution of the B cell repertoire following B cell depletion with more autoreactive cells.

Atacicept

Atacicept is a chimeric molecule with the extracellular domain of TACI, which binds both BAFF and APRIL, a proliferation-inducing ligand fused to the constant region of human IgG1. In a Phase I trial in patients with SLE, atacicept was well tolerated.[25] However, a Phase II study of atacicept plus mycophenlyate in patients with lupus nephritis was terminated because of an increased number of infections.[26] A Phase II/III trial of atacicept for non-renal lupus with less immunosuppressive concomitant therapy is ongoing.[27] Atacicept is of interest in autoantibody mediated diseases because of its profound effects on plasma cells, but its use leads to significant decreases in Ig levels, including both IgM and IgG.

TARGETING CO-STIMULATORY SIGNALING PATHWAYS

CD40 binding to CD40 ligand is one of the most important co-stimulatory signals on B cells inducing activation, proliferation, and class switching. Neutralizing CD40L can interfere with germinal center reactions and will also diminish activation of marginal zone B cells. Direct inhibition of collaboration between B and T cells through inhibition of the CD40–CD40L pathway has been demonstrated to be effective in mouse models of lupus.[28,29]

Two studies of anti-CD40L antibodies in SLE have been reported. The first open-label study (Biogen Hu5c9 antibody) was discontinued because of unexpected thromboembolic events.[30] The second double-blind, placebo-controlled trial (IDEC 131) of 85 patients with mild to moderate SLE failed to show clinical efficacy over placebo, perhaps due to insufficient blockade.[31] Moreover, use of this anti-CD40L antibody in a separate study in Crohn's disease was again associated with thrombotic events.

Additional controlled studies are warranted to understand the mechanism of action of this therapy. New reagents to block the CD40–CD40L pathway but not exhibit thrombogenic properties are in development.

Alternative co-stimulatory targets in SLE include **CD28 and CTLA4 receptors and their B-cell co-ligands B7-1 and B7-2**. Blockage of B7 stimulation on B cells with a fusion protein of the extracellular domain of CTLA and the immunoglobulin constant region (abatacept) has yielded promising results in murine SLE[32] and demonstrated safety in human clinical trials in RA and psoriasis. There are two ongoing clinical trials in SLE, both in lupus nephritis.

ICOS (inducible costimulator)/ ICOS-L (inducible costimulator ligand)

The inducible costimulator (ICOS) is a T cell-specific molecule structurally and functionally related to CD28. ICOS is induced on the T cell surface following cell activation. It transmits

signals that are co-stimulatory for T cells. ICOS and its ligand has a significant role in T cell-B cell interaction and B cell differentiation, both in mice and in humans. It was reported that there is an increased expression of ICOS on CD4+ as well as CD8+ T cells in SLE. Moreover, ICOS-L is down regulated in a high percentage of peripheral blood memory B cells upon physical interaction with ICOS (occurring in specific phases of B cell differentiation). ICOS is one of the forces driving the formation of memory B cells and plasma cells in SLE and is therefore a potential therapeutic target in SLE. ICOS-L blockade in a murine model of lupus nephritis is a promising therapeutic modality.[33]

CD4+ T cell populations in SLE patients have been analyzed for the expression of co-stimulatory markers other than ICOS. Expression of co-stimulatory molecules CD80 and CD134 on CD4+ T cells were significantly higher in lupus nephritis patients and correlated with SLE disease activity.[34] Targeting these co-stimulatory molecules could be a new therapeutic approach in patients with lupus nephritis. Activated T cells express ICOS, which binds to B7RP1 (B7-related peptide 1). B7RP1 is proposed to inhibit development of T_{FH} cells, which help B cells in the germinal centers. A fully humanized anti-B7RP1 antibody (AMG557) is in phase I trials in patients with SLE.

ANTI-CYTOKINE THERAPY

The alternate way to directly target immune cells is to interfere with their messengers. Immune cells exert many of their effector and immunoregulatory functions by cytokine release. Most cytokines investigated have been found to be dysregulated in SLE.

Tumor necrosis factor (TNF) and anti-TNF therapy

TNF is a pleiotropic cytokine that exerts several functions in the immune system and can either promote or reduce autoimmunity. Therapeutic TNF blockade in patients with autoimmune diseases, such as rheumatoid arthritis (RA) or Crohn's disease is associated with the development of ANA, anti dsDNA, and anti-cardiolipin antibodies, as well as with rare cases of drug-induced lupus like syndromes, all of which disappear after therapy is discontinued. TNF concentration is increased in sera of SLE patients and is associated with disease activity.[35] The short term use of TNF blockade might be safe and effective in some SLE patients, especially those with lupus nephritis.[36,37]

Anti-IL-10

IL-10 is the first cytokine successfully blocked in SLE. IL-10 is increased in serum of patients with SLE and is associated with disease activity.[38] IL-10 is over-produced by B cells of patients with SLE and is implicated in B cell activation.[39] On the other hand, IL-10 has potent suppressive effects on antigen presenting cells and can directly suppress T cells.[40] IL-10, however, is also considered to be anti-inflammatory and its presence in SLE may not be a major component of disease pathogenesis.

In an open label pilot study, a single dose of mouse anti-IL-10 mAb (B-N10) is given to 6 patients with active, steroid-dependent SLE.[41] There was improvement in cutaneous lesions, joint symptoms and disease activity. Prednisone dose was also decreased. The beneficial effect lasted 3–6 months. All patients developed antibodies against the mouse mAb. Currently, there are no studies with humanized anti-IL-10 mAb.

Anti-IL-1

IL-1 can be increased by TNF and by autoantibodies to dsDNA. Serum IL-1 level is increased with lupus disease activity. A low level of IL-1 receptor antagonist (IL-1Ra) is seen in lupus nephritis.[42] Anakinra is used as an alternative in individual patients with

lupus arthritis not responding to conventional treatments. There are two small, open-label trials of IL-1 receptor antagonist Anakinra in patients with SLE and severe lupus polyarthritis, both of which showed beneficial effects.[43] In one of them, 2 out of 4 patients relapsed while on Anakinra.[43,44] In the second study with 3 patients, there was a transient improvement of arthritis but no effect on muscle pain.[44] Currently, there are no ongoing trials in lupus nephritis.

Anti-IL-18

IL-18 is a pro-inflammatory cytokine closely related to IL-1. Several groups have observed increased serum levels of IL-18 in SLE, which appears to be associated with the TNF level.[45] IL-18 is over-expressed in the nephritic kidneys of MRL/lpr mice. Moreover, MRL/lpr mice benefit from targeting IL-18.[46] To date, IL-18 blockade has not been used in SLE patients.

Anti-IL-6

IL-6 is another pro-inflammatory cytokine secreted predominantly by macrophages, DCs, T and B cells and is increased in SLE serum.[47,48] IL-6 is also highly expressed in lupus nephritis. It activates B cells and drives plasma-cell differentiation. It also facilitates the differentiation of Th17 and T follicular helper cells. IL-6 is induced in DCs by nucleic acid containing immune complexes as well as by multiple cytokines including TNF, IL-1, and IFNγ. In NZB/W mice, IL-6 promotes disease, and anti-IL-6 therapy delays lupus nephritis,[49] suggesting that IL-6 blockade might also be beneficial in SLE patients.

Tocilizumab is a humanized IgG1 Ab directed to human IL-6 receptor which inhibits IL-6 signalling. An open-label, dose-escalating phase I study of tocilizumab in SLE showing safety has recently been published[50] and a larger study is scheduled.

Anti-IL-15

IL-15 is increased in 40% of patients with SLE but it IL-15 is mainly produced by the macrophage/ monocyte cell line. It is not directly associated with disease activity. IL-15 may be responsible for some immune abnormalities of the disease, such as stimulating lymphocytic expression of Bcl-2 and CD25 (in both B and T cells).[51] Therapeutic agents against IL-15 are currently being tested in other autoimmune diseases.

Eculizumab (anti-C5 mAb) was evaluated in Phase I study in SLE patients and led to no significant clinical improvement.[52] Eculizumab, however, has been approved by the FDA for paroxysmal nocturnal hemoglobinuria to reduce hemolysis.

Memantine

A subset of anti-DNA antibodies that can be found in sera of 30 to 50% of lupus patients, cerebrospinal fluids (CSF), especially CSF of patients with central nervous system (CNS) manifestations of lupus, and lupus brain tissue bind also to NMDA receptors and mediate excitotoxic neuronal death. This causes no significant neuronal damage when present in the circulation unless there is a breakdown in the blood- brain barrier (BBB). When the anti-NMDA-receptor antibodies are present in CSF of patients with CNS lupus[53], they correlate with CNS symptoms. Memantine is an NMDA receptor antagonist that can protect neurons from antibody-mediated death. One small study of Memantine failed to show improvement in cognitive function in SLE patients but the study was of short duration, the patients were not selected for antibody positivity and the assessment of cognitive function was subjective.

Interferon-alpha (IFN-α)

Abundant studies suggest that activation of type I IFN plays a role in driving the autoimmune process in SLE. Findings of elevated serum levels of IFN-α in SLE patients, IFN signature in gene expression profiling of SLE peripheral blood mononuclear cells (PBMCs), and the fact that SLE serum is able to induce maturation of DCs in an IFN-α dependent fashion all demonstrate the importance of IFN in SLE. Several recent studies in mice have confirmed the contribution of IFN-α to disease pathogenesis. In addition to DC activation, IFN-α has been associated with B-cell lymphopenia, germinal center differentiation, and generation of plasma cells, findings of obvious relevance to B-cell abnormalities characteristic of SLE. Thus, IFN-α is an attractive therapeutic target. MEDI-545 is a fully human mAb targeting IFN-α. Recent data from an ongoing Phase 1 clinical trial suggests that neutralizing monoclonal antibody against IFN-α can ameliorate disease activity.[54]

Plasmapheresis (or plasma exchange) is a controversial treatment modality for severe SLE. It mediates the physical removal of pathogenic autoantibodies, immune complexes and circulating inflammatory mediators such as activated complement components. Plasmapheresis failed to show a benefit in lupus nephritis several studies in the 1990s and an antibody rebound phenomenon was often noted after plasmapheresis. Plasmapheresis may have a role in the management of some less common complications of SLE such as thrombotic thrombocytopenic purpura, cryoglobulinemia and hyperviscosity,[55] but most regimens now include immunosuppressive agents to prevent antibody rebound.

Intravenous immunoglobulin (IVIG)

IVIG is a blood product prepared from plasma of multiple individuals. High dose immunoglobulin has immunomodulatory properties. The exact mechanism of action of IVIG is not clear yet although there are numerous proposed mechanisms of action of IVIG in SLE. These are idiotype network regulation, modulation of immune complex deposition and complement regulation.[56] IVIG also suppresses the activation of B lymphocytes through enhancing expression of Fc gamma receptor (FcγR) on B cells and DCs. [56,57] Interaction between Fc fragment of IgG and FcγR on target cells appears to be essential for many anti-inflammatory effects and in B cells. Cross-linking the BCR to the FcRIIB is responsible for decreasing antibody production. There are no large randomized clinical trials looking at the efficacy of IVIG in SLE. There are small clinical trials, case series, and case reports in the literature supporting its use in SLE patients with arthritis, fever, thrombocytopenia[58,59], neuropsychiatric SLE[59,60], myocarditis[61], cardiac tamponade[62], end-stage renal disease[63], chorea[64], polyradiculopathy[65], myelofibrosis[66], pneumonitis[67], membranous or membranoproliferative lupus nephritis[68]. There is a pilot study showing temporary beneficial effects in mildly to moderately active SLE.[69] There is no role for IVIG as a first-line treatment in SLE, but it may be an alternative treatment modality in difficult to treat cases and cases with concomitant sepsis.

DNA vaccination

DNA vaccination is being evaluated as a procedure to induce immune tolerance in autoimmune disease.[70] It relies on the injection of a gene encoding for a target protein with the goal of eliciting a potentially tolerogenic immune response in the host. DNA vaccination has been successful in protecting mice from the development of organ-specific autoimmunity, experimental allergic encephalomyelitis (EAE), autoimmune diabetes, experimental arthritis, experimental uveitis as well as SLE and antiphospholipid syndrome. Choosing the most appropriate vector for gene transfer is still difficult. The degree of protection is influenced by the capacity of DNA vaccination to modulate immune responses affecting the T helper subsets and, importantly, the T cell immunoregulatory subsets.

It has been demonstrated that T cells that recognize an Ig consensus sequence presented by B cells can modulate lupus-like disease in mice. NZB/W F1 lupus-prone mice were given B cells with a DNA plasmid encoding a consensus sequence from murine anti-DNA IgG fused to the F_c region of IgG or with control plasmids. The conjugation of the peptide with the Ig F_c portion conferred structural stability to the peptide and localized the transgenic construct to endosomes, allowing optimal processing and presentation. This approach efficiently protected mice from SLE, increased survival and reduced severity of nephritis.[71] Studies suggest that expression of the anti-DNA Ig consensus sequence induced immunoregulatory T cells that disease expression diminished.[71]

Statins

As we have learned more about the immunomodulatory effects of statins, they have been evaluated as therapeutic agents for autoimmune diseases. Statins inhibit the production of proinflammatory mediators such as TNF-α, IL-1β, IL-6, IL-8, RANTES, monocyte chemotactic protein 1 (MCP-1), IL-17, cyclooxygenase 2, and nitric oxide by T cells and antigen-presenting cells. Both in vitro and in vivo studies suggest that statins promote the secretion of T_h2 cytokines, including IL-4, IL-5, IL-10, and transforming growth factor β (TGFβ).{Dunn, 2006 #48} Statins seem to suppress IFN transduction pathways and IFNγ-induced major histocompatibility complex class II (MHC-II) expression in various cell types. Statin-induced repression of MHC-II also represses MHC-II–dependent activation of T cells. Statins also decrease the expression of costimulatory and adhesion molecules. {Dunn, 2006 #48}

Statins may also play an important role in prevention of cardiovascular diseases in SLE patients. In addition to their effects on the suppression of cholesterol synthesis, statins have direct effect on endothelium, plaque formation, and thromboxane synthesis. Statins are also reported to have antithrombotic/ anti-inflammatory effects on antiphospholipid syndrome (APS) patients.[72] A recent controlled study **(not placebo controlled)** demonstrated a reduction in SLE disease activity (SLEDAI) after atorvastatin therapy in addition to the improvement of the endothelial-dependent vasodilatation in SLE patients after 8 weeks.[73] Another statin, simvastatin, also led to a similar reduction in disease activity in female patients.[74] A 1-year trial with atorvastatin demonstrated a decrease in cholesterol levels, proteinuria, and rate of progression of chronic kidney disease in SLE patients with lupus nephritis.[75]

In another study, there were no significant effects of fluvastatin on cardiac events in renal transplant recipients with SLE.{Norby, 2009 #44} Thus, we need multicentre and prospective studies to see whether and which statin treatment in SLE patients is associated with a decrease in cardiovascular morbidity and mortality and has an effect on systemic and organ specific inflammation.

Antioxidants: N-acetylcysteine (NAC), Cysteamine (CYST)

Antioxidants may be a beneficial adjunctive therapy in the treatment of SLE. Reactive oxygen intermediates (ROIs), the superoxide anion, hydroxyl radicals and hydrogen peroxide, are generated during immune processes associated with neutrophil and macrophage activity. ROIs directly damage endothelium, leading to vascular permeability and edema. They also oxidize cell membrane lipids and induce apoptosis. Moreover, ROIs also activate immune cells through effects on intracellular messenger systems. In contrast, antioxidants reduce the damaging effects of ROIs.

In a study testing the immunomodulatory effects of the non-enzymatic antioxidants, N-acetylcysteine (NAC) and cysteamine (CYST), on glomerulonephritis, and mortality in the

NZB/W F1 mouse model of SLE, significant benefit was observed. NAC suppressed autoantibody formation and prolonged survival. CYST inhibited the development of renal insufficiency and improved survival significantly.[76] Thus, antioxidants may be a beneficial adjunctive therapy in the treatment of SLE and are being evaluated in an ongoing clinical trial.

Anti-IgE antibodies and Anti-FcЄRIα antibodies

Human IgE molecules bind specifically and with very high affinity to receptors (FcЄRI) on the surface of human basophils and mast cells. IgE autoantibodies are found in the serum of patients with autoimmune diseases such as rheumatoid arthritis, SLE[77], and systemic sclerosis[78] an can activate mast cells and basophils. Antigen will interact with membrane-bound IgE, causing cross-linking of the receptor with subsequent degranulation of basophils and mast cells. Furthermore, basophils increase their expression BAFF when activated by immune complexes containing IgE antibodies and so contribute to a loss of B cell tolerance.

Thus, the IgE-FcЄRI network has potential to be a novel theurapeutic target in SLE. Moreover, cross-linking of FcЄRI with FcγRIIb leads to inhibition of basophil degranulation[79], suggesting another therapeutic target in SLE focusing IgE antibodies.

Syk (spleen tyrosine kinase) inhibition

Spleen tyrosine kinase (Syk) is a member of the Src family of nonreceptor tyrosine kinases. Syk is involved in signal transduction pathways in various cells and is widely expressed in the hematopoietic system as well as immune cells. Syk is overexpressed in T cells from SLE patients. It has been shown that inhibition of Syk by the small molecule SyK inhibitor, fostamatinib (R788) reverses aberrant T cell signaling, inhibits progression of kidney disease and also improves disease manifestations in NZB/W F1 lupus-prone mice.[80]. This drug has also been shown to prevent development of skin disease and significantly reduce established skin disease in MRL/lpr mice. Syk inhibition also reduced the size of spleen and lymph nodes, suppressed development of renal disease, and suppressed established renal disease. After the treatment is discontinued, the beneficial effects continued for another 4 weeks for renal disease and at least 8 weeks for skin disease[81]. Syk inhibition resulted in prompt clinical improvement in rheumatoid arthritis patients in a Phase II study.[82] It was also beneficial in idiopathic thrombocytopenia.[83] Syk inhibition may be a valuable treatment for patients with SLE.

Jak (Janus kinase) inhibition

The Janus family kinases (Jaks), Jak1, Jak2, Jak3 and Tyk2, are a subgroup of the non-receptor protein tyrosine kinases. They are involved in cell growth, survival, development and differentiation of a variety of cells, but are critically important for immune cells and hematopoietic cells. Jaks mediate multiple signaling events in innate and adaptive immune system. There are clinical trials with JAK3 inhibitor CP 690, 550 in psoriasis, rheumatoid arthritis (RA), and kidney transplantation. In a Phase 2A randomized, double-blind, placebo-controlled study of RA patients who had previously failed therapy, CP690, 550 demonstrated an ACR20/50/70 response was 80/33–54/13–28%, respectively. Dose-dependent neutropenia and anemia were observed. There are ongoing studies assessing the safety and efficacy of CP-690, 550 compared with placebo in combination with methotrexate and in comparison to TNF blockade. R348, another JAK3 inhibitor, is in Phase 1 trial in RA. It still needs to be determined whether JAK3 antagonists are acting on T or B cells or both and if T cells, on which subset of T cells. JAK3 is important for IL-21 signalling, but whether Th17 cells are blocked by JAK3 antagonists remains a question. Moreover, it remains critical to monitor the toxicities of these agents. Nevertheless, they exhibit strong potential for therapy of autoimmune diseases.

SUMMARY

In this review article, the general approach to treatment of SLE, focusing on current approved therapies, ongoing clinical trials, treatment successes and failures, novel approaches that has a potential to be used in the future are discussed in detail. Advances in our understanding of the mechanisms of SLE have offered better drug targets for treatment. Several important questions remain such as what the initiating stimuli for autoimmunity are and how cascade of events promote disease flare. The answers to these questions may lead to early diagnosis of SLE and early therapeutic intervention, which might increase the chances to go into remission and improve prognosis and quality of life as well as life expectancy in the long run. Biomarkers which will help us to identify SLE disease and disease activity earlier are urgently needed. Future therapies will take advantage of our expanding knowledge of the pathogenesis of SLE.

Over the next several years, we will test the efficacy of many new therapeutic agents. What is most important is that we learn to subset patients with respect to genetic susceptibility, pathogenetic mechanism, and phase of disease so that we maximize the therapeutic effect of each agent and minimize its toxicity. This represents a formidable challenge but one that is critical to improving outcome for individuals with SLE.

What Do We Know?

- SLE is an autoimmune disease involving multiple organ systems, with recurrent flares causing progressive damage and disability. SLE is a clinically heterogeneous disease.
- Both the innate and the adaptive immune system are dysregulated in SLE.
- Antimalarials, anti-inflammatory drugs, and immunosuppressive drugs have been the basis for SLE therapy over the past 30 years.
- These are golden days in the development of drugs for SLE. There are many ongoing clinical trials in lupus patients with theurapeutics having different mechanisms of action, such as classical immunosuppressant, cell depletion, antigen-specific immunomodulation and targeting of antigen-nonspecific, immune- activating molecules.
- Multiple susceptibility genes have been identified that help identify therapeutic targets and may ultimately help identify at risk individuals.

What is still unknown?

- Better and targeted therapies with fewer side effects are needed in SLE.
- Combination therapy with different biologic agents could potentially provide better efficacy by synergistically targeting different arms of the immune system.
- There is an urgent need for nonimmunosuppressive therapy.
- We need better tools to predict the best time for optimal treatment of SLE.
- New agents that block cell surface-bound BAFF or that bind both BAFF and APRIL may improve efficacy, as might combining BAFF blockade with B-cell depletion therapy.
- There are difficulties in patient subsetting, trial design, current disease activity measurement tools and the proper use of combination therapies that may limit our ability to discern clinical benefit.

Abbreviations used

APRIL	a proliferation-inducing ligand
BAFF	B cell lymphocyte activating factor
BCR	B cell receptor
CNS	central nervous system
CSF	cerebrospinal fluid
DC	dendritic cell
IFN	interferon
NMDA	N-methyl-D-aspartate
pDC	plasmacytoid dendritic cells
SLE	Systemic lupus erythematosus
TACI	transmembrane activator and calcium-modulator and cyclophilin ligand interactor
TLR	toll-like receptor

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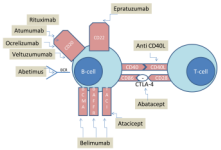

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Table 1

Summary of Treatments and Clinical Trials in treatment of SLE

Molecular Target	Drug(s)	Stage of Clinical Trial	Result(s)	Reference(s)
Immune Cell Targeted Therapies				
Anti-CD20	Rituximab	Phase II/III EXPLORER and LUNAR trial	Failed to meet primary and secondary endpoints	15,16
Anti-CD20	Ocrelizumab	Phase III	Terminated due to infectious complications	
Anti-CD22	Epratuzumab	Phase IIb	Inadequate information to evaluate study	18,19
B cell tolerogen	Abetimus (LJP-394)	Phase III ASPEN trial	Terminated after interim efficacy analysis	21,22
BAFF-R, BCMA, TACI	Belimumab	Phase III BLISS-52 and -76	Recommended by FDA Advisory Commitee	23,24
TACI	Atacicept	Phase II for Lupus nephriti	Terminated due to infectious complications	26
	Atacicept	Phase II/III for non-renal lupus	ongoing	27
Co-stimulatory Signaling Pathways				
CD40-CD40L	Anti-CD40L Ab (Biogen Hu5c9 antibody)	Terminated	Terminated due to thromboembolic complications	30
CD28 and CTLA4 receptors and co-ligands	Abatacept	Phase II trial (for Lupus nephritis)	Ongoing	----
ICOS- B7RP1	Anti-B7RP1 Ab (AMG557)	Phase I	Ongoing	----
Anti-cytokine Therapy				
IL-10	Anti-IL10 mAb (B-N10)	Pilot study showed beneficial effects	No ongoing trials with humanized anti- IL10 mAb	41
IL-1	Anakinra (IL-1 Ra)	2 small open label trials	No ongoing trials	43,44
IL-18	IL-18 blockade	Only mouse studies	No human trials	----
IL-6	Tocilizumab	Phase I	Larger study is scheduled	50
IL-15			No trials in SLE	
Other Treatments				
Complement 5	Eculizumab (anti-C5 mAb)	Phase I	No improvement in SLE	52
NMDA receptor antagonist	Memantine	Pilot study failed to improve cognitive function	No ongoing trials	----
IFN-α	MEDI-545	Phase I trial	Ongoing	54
ROI (Reactive Oxygen Intermediates)	N-Acetylcysteine (NAC), Cysteamine (CYST)	Beneficial effect in mice	Ongoing clinical trial in human	----
IgE and FcЄRIα	Antibodies	No trials yet		
Syk (spleen tyrosine kinase)	Fostamatinib (R788)	Phase II study in RA	No trials in SLE yet	80,81,82
Jak (Janus kinase)	CP 690, 550 (JAK3inhibitor)	Clinical trials in psoriasis, RA and kidney transplantation	No trials in SLE yet	----