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Current and novel therapeutics in the treatment of systemic lupus erythematosus

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Activity Objectives

1. To list and define the action of drugs targeting systemic inflammation in patients with lupus.
2. To list and define the action of drugs specifically directed against immune cells that are being investigated for the treatment of lupus.
3. To list and define the action of drugs that target costimulatory signaling pathways.

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Systemic lupus erythematosus (SLE) is a complex autoimmune disease with significant clinical heterogeneity. Recent advances in our understanding of the genetic, molecular, and cellular bases of autoimmune diseases and especially SLE have led to the application of novel and targeted treatments. Although many treatment modalities are effective in lupus-prone mice, the situation is more complex in human subjects. 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. (J Allergy Clin Immunol 2011;127:303-12.)

Key words: *Systemic lupus erythematosus, treatment*

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 antimalarial drugs, steroidal and nonsteroidal anti-inflammatory agents, and immunosuppressive drugs, including cyclophosphamide, azathioprine, mycophenolic acid, and methotrexate. Although there is a dramatic improvement in the prognosis for patients with SLE, 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.

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SYSTEMIC INFLAMMATION-DIRECTED TREATMENT

Antimalarial drugs–hydroxychloroquine

Antimalarial drugs remain the 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] Antimalarial drugs inhibit phagosome function, thereby inhibiting Toll-like receptor

Abbreviations used
APRIL: A proliferation-inducing ligand
BAFF: B-cell lymphocyte-activating factor
BCR: B-cell receptor
BLyS: B-lymphocyte stimulator
B7RP1: B7-related peptide 1
CD40L: CD40 ligand
CNS: Central nervous system
CSF: Cerebrospinal fluid
DC: Dendritic cell
ds: Double stranded
FDA: US Food and Drug Administration
ICOS: Inducible costimulator
Jak: Janus kinase
MMF: Mycophenolate mofetil
NMDA: N-methyl-D-aspartate
RA: Rheumatoid arthritis
ROI: Reactive oxygen intermediate
SLE: Systemic lupus erythematosus
Syk: Spleen tyrosine kinase
TACI: Transmembrane activator and calcium modulator and cyclophilin ligand interactor
TLR: Toll-like receptor

(TLR) activation, leading to a downregulation 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]

Corticosteroids

Glucocorticoids are the mainstay of treatment in patients with 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 nuclear factor κB activity.[5] In patients with lupus, glucocorticoids are typically administered orally on a daily basis. When doses greater than 60 mg/d are required, patients can receive intravenous methylprednisolone pulse therapy (30 mg/kg; maximum, 1 g/d), although such treatment has not been shown to be more effective than doses of 100 to 200 mg daily and might increase toxicity. Recently, it was demonstrated, both *in vitro* and *in vivo*, that stimulation of plasmacytoid dendritic cells (DCs) through TLR7 and TLR9 can account for a reduced activity of glucocorticoids to inhibit the IFN pathway in patients with SLE and in 2 lupus-prone murine strains. It is therefore possible that inhibitors of TLR7 and TLR9 signaling could be effective corticosteroid-sparing drugs.[6]

Cyclophosphamide

Pulse cyclophosphamide 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 "minipulse" cyclophosphamide with conventional pulse cyclophosphamide therapy (National Institutes of Health trials) showed no difference in efficacy between the groups, as defined by the frequency of renal deterioration or death, mean serum creatinine level, 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 (MMF), because of their greater safety. Cyclophosphamide is also used with corticosteroids in patients with severe neuropsychiatric involvement.

MMF

This immunosuppressive drug has been used for several years in cases of human organ transplantation. 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 with cyclophosphamide in a number of case series for the treatment of lupus nephritis. In an open-label study comparing MMF and pulse cyclophosphamide as induction therapy for lupus nephritis, MMF was found to be more efficacious than cyclophosphamide.[8] The main side effects of MMF were gastrointestinal events, such as diarrhea, nausea, and vomiting; minor infectious episodes; and rare cases of leukopenia. In another study MMF was as effective as pulse cyclophosphamide in maintaining renal response and caused fewer serious adverse events.[9] Results of a large multinational trial examining the efficacy of MMF compared with that of intravenous cyclophosphamide over 6 months as induction therapy and either MMF or azathioprine as maintenance therapy in patients with lupus nephritis for 36 months were comparable in the MMF and cyclophosphamide 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 azathioprine.

Azathioprine

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

Methotrexate

Methotrexate is a folic acid analogue and a potent competitive inhibitor of dihydrofolate reductase and acts through inhibition of both DNA and RNA synthesis. Methotrexate has a role in the management of resistant arthritis and skin disease in patients with SLE as a steroid-sparing agent. It does not have a role in the treatment of patients with SLE 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, 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 costimulatory molecules, and inhibition of cytokines with direct B-cell effects.

Agents that target B cells are the mAbs rituximab, ofatumumab, ocrelizumab and veltuzumab (anti-CD20), epratuzumab (anti-CD22), belimumab (anti–B-cell lymphocyte-activating factor [BAFF]), and atacicept (anti-BAFF and a proliferation-inducing ligand [APRIL]) (Fig 1).

Anti-CD20 (rituximab) is a chimeric murine/human mAb against the B cell–specific antigen CD20.[11] It was approved by the US Food and Drug Administration (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, type I diabetes, anti-neutrophil cytoplasmic antibody–positive vasculitis, IgM antibody–associated polyneuropathy, idiopathic thrombocytopenic purpura, 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 naive and memory B-cell stages. In human subjects 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 including patients with severe refractory SLE (n = 7) suggested that retreatment with rituximab is safe and that clinical response is sustained up to 12 months on average.[13] Rituximab also showed promising efficacy in patients with refractory neuropsychiatric manifestations of SLE. Unfortunately, the placebo-controlled phase II/III study to Evaluate the Efficacy and Safety of Rituximab in Patients with Severe Systemic Lupus Erythematosus (EXPLORER) and Lupus Nephritis Assessment with Rituximab (LUNAR) trials of rituximab in patients with SLE failed to meet the primary and secondary end points.[15,16]

Other anti-CD20 mAbs are of atumumab, ocrelizumab and veltuzumab. A phase III study with ocrelizumab (in addition to prednisolone, low-dose cyclophosphamide, and MMF or azathioprine) in patients with lupus nephritis was terminated because of infectious complications.

Anti-CD22 (epratuzumab)

Epratuzumab is an mAb against CD22, a B cell–specific surface antigen involved in the modulation of BCR signaling.[17] It causes a modest 35% to 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 placebo-treated patients. A "combined index end point" was used as the primary outcome measure. The details of this index were not released, but it primarily measured British Isles Lupus Assessment Group index 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 cross-link 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 nonrenal lupus and lupus nephritis. It contains 4 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 the abetimus molecule. However, other trials failed to show any difference between treated and untreated groups in the 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 Abetimus Sodium in Patients with a History of Lupus Nephritis (ASPEN) trial, the trial was terminated when interim efficacy analysis indicated it would be futile to continue.[21,22]

BAFF blockade belimumab

Belimumab is a fully human mAb that binds to and inhibits action of the soluble form of the B-lymphocyte stimulator (BLyS; also known as BAFF), a B cell survival factor for B cells from the transition stage up to the plasma cell stage. When belimumab is bound to the soluble form of BLyS, it prevents BLyS from binding to the receptors transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), B-cell maturation antigen, and BAFF receptor. BAFF levels are increased in many patients with SLE 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 end point of improvement in the Safety of Estrogen in Lupus Erythematosus National Assessment SLE Disease Activity Index score at week 52, clinical data from the phase II trial were used to develop an SLE response index. Two large phase III studies of Belimumab in Subjects with Systemic Lupus Erythematosus (BLISS), BLISS-52 and BLISS-76, demonstrated significant clinical efficacy of belimumab, although benefit was not sustained at week 76.[23,24] The biological activity of belimumab was also demonstrated; the total number of B cells, naive B cells, plasmablasts, and 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 FDA's 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. Increases in BAFF levels lead to macrophage activation and promote survival of autoreactive B cells. Combining BAFF inhibition and B-cell depletion might have a synergistic effect and prevent a reconstitution of the B-cell repertoire after 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, 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 mycophenolate in patients with lupus nephritis was terminated because of an increased number of infections,[26] presumably because plasma cells require APRIL and so serum Ig was reduced. A phase II/III trial of atacicept for nonrenal 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 immunoglobulin levels, including both IgM and IgG.

TARGETING COSTIMULATORY SIGNALING PATHWAYS

CD40 binding to CD40 ligand is one of the most important costimulatory signals on B cells, inducing activation, proliferation, and class switching. Neutralizing CD40 ligand (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 murine models of lupus.[28,29]

Two studies of anti-CD40L antibodies in patients with 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 because of insufficient blockade.[31] Moreover, use of this anti-CD40L antibody in a separate study in patients with Crohn 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 costimulatory targets in patients with SLE include CD28 and cytotoxic T lymphocyte–associated antigen 4 receptors and their B-cell coligands B7-1 and B7-2. Blockade of B7 stimulation on B cells with a fusion protein of the extracellular domain of cytotoxic T lymphocyte–associated antigen and the immunoglobulin constant region (abatacept) has yielded promising results in murine SLE[32] and demonstrated safety in human clinical trials of RA and psoriasis. There are 2 ongoing clinical trials in patients with SLE, both in lupus nephritis.

The inducible costimulator (ICOS) is a T cell–specific molecule structurally and functionally related to CD28. ICOS is induced on the T-cell surface after cell activation. It transmits signals that are costimulatory for T cells. ICOS and its ligand have a significant role in T-cell–B-cell interaction and B-cell differentiation both in mice and human subjects. It was reported that there is an increased expression of ICOS on $CD4^+$ and $CD8^+$ T cells in patients with SLE. Moreover, ICOS ligand is downregulated in a high percentage of peripheral blood memory B cells on 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 patients with SLE and is therefore a potential therapeutic target. ICOS ligand blockade in a murine model of lupus nephritis is a promising therapeutic modality.[33]

$CD4^+$ T-cell populations in patients with SLE have been analyzed for the expression of costimulatory markers other than ICOS. Expression of the costimulatory molecules CD80 and CD134 on $CD4^+$ T cells was significantly higher in patients with lupus nephritis and correlated with SLE disease activity.[34] Targeting these costimulatory molecules could be a new therapeutic approach in patients with lupus nephritis. Activated T cells express ICOS, which binds to B7-related peptide 1 (B7RP1). B7RP1 is proposed to inhibit development of T follicular helper 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 through cytokine release. Most cytokines investigated have been found to be dysregulated in patients with SLE.

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 RA or Crohn disease, is associated with the development of antinuclear antibody and anti-dsDNA and anticardiolipin antibodies, as well as with rare cases of drug-induced lupus-like syndromes, all of which disappear after therapy is discontinued. TNF concentrations are increased in sera of patients with SLE and are associated with disease activity.[35] The short-term use of TNF blockade might be safe and effective in some patients with SLE, especially those with lupus nephritis.[36,37]

Anti–IL-10

IL-10 is the first cytokine successfully blocked in patients with SLE. IL-10 levels are increased in sera of patients with SLE and are associated with disease activity.[38] IL-10 is overproduced 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 patients with SLE might not be a major component of disease pathogenesis.

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

Anti–IL-1

IL-1 levels can be increased by TNF and by autoantibodies to dsDNA. The serum IL-1 level is increased with lupus disease activity. A low level of IL-1 receptor antagonist is seen in patients with lupus nephritis.[42] Anakinra is used as an alternative in individual patients with lupus arthritis not responding to conventional treatments. There are 2 small open-label trials of the IL-1

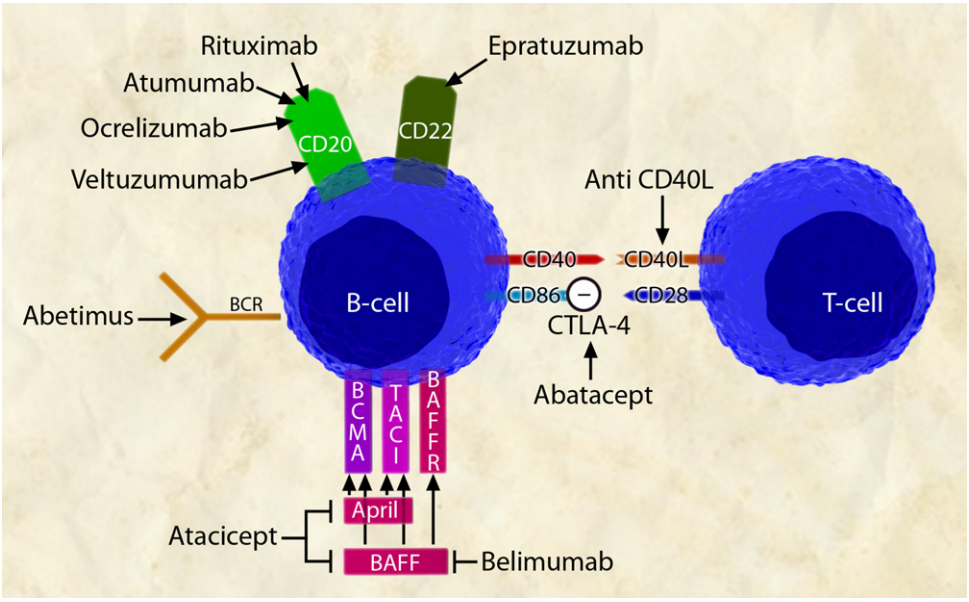

FIG 1. B cell costimulatory molecules and receptors for the survival factors BAFF and APRIL are shown as well as cell surface molecules being targeted therapeutically. The therapeutic agents are identified along with their targets. *BCMA*, B-cell maturation antigen; *CTLA-4*, Cytotoxic T lymphocyte–associated antigen 4.

receptor antagonist anakinra in patients with SLE and severe lupus polyarthritis, both of which showed beneficial effects.[43,44] In one of them, 2 of 4 patients relapsed while receiving anakinra.[43] In the second study with 3 patients, there was a transient improvement of arthritis symptoms but no effect on muscle pain.[44] Currently, there are no ongoing trials in patients with lupus nephritis.

Anti–IL-18

IL-18 is a proinflammatory cytokine closely related to IL-1. Several groups have observed increased serum levels of IL-18 in patients with SLE, which appear to be associated with TNF levels.[45] IL-18 is overexpressed 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 patients with SLE.

Anti–IL-6

IL-6 is another proinflammatory cytokine secreted predominantly by macrophages, DCs, and T and B cells and is increased in sera from patients with SLE.[47,48] IL-6 is also highly expressed in patients with lupus nephritis. It activates B cells and drives plasma cell differentiation. It also facilitates the differentiation of T_H17 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 IFN-γ. 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 patients with SLE.

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

Anti–IL-15

IL-15 levels are increased in 40% of patients with SLE, but it is mainly produced by the macrophage/monocyte cell line. It is not directly associated with disease activity. IL-15 might 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 a phase I study in patients with SLE 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 patients with lupus, cerebrospinal fluid (CSF), especially CSF of patients with central nervous system (CNS) manifestations of lupus, and lupus brain tissue bind also to N-methyl-D-aspartate (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.

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 patients with SLE, but the study was of short duration, the patients were not selected for antibody positivity, and the assessment of cognitive function was subjective.

IFN-α

Abundant studies suggest that activation of type I IFN plays a role in driving the autoimmune process in patients with SLE.

TABLE I. Summary of treatments and clinical trials in the 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 end points	15,16
Anti-CD20	Ocrelizumab	Phase III	Terminated because of 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 receptor, BCMA, TACI	Belimumab	Phase III BLISS-52 and BLISS-76	Recommended by FDA Advisory Committee	23,24
TACI	Atacicept	Phase II for lupus nephritis	Terminated because of infectious complications	26
	Atacicept	Phase II/III for nonrenal lupus	Ongoing	27
Costimulatory signaling pathways				
CD40-CD40 ligand	Anti-CD40L antibody (Biogen Hu5c9 antibody)	Terminated	Terminated because of thromboembolic complications	30
CD28 and CTLA-4 receptors and coligands	Abatacept	Phase II trial (for lupus nephritis)	Ongoing	—
ICOS-B7RP1	Anti-B7RP1 antibody (AMG557)	Phase I	Ongoing	—
Anti-cytokine therapy				
IL-10	Anti–IL-10 mAb (B-N10)	Pilot study showed beneficial effects	No ongoing trials with humanized anti–IL-10 mAb	41
IL-1	Anakinra (IL-1Ra)	Two small open-label trials	No ongoing trials	43,44
IL-18	IL-18 blockade	Only murine 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	N-Acetylcysteine, cysteamine	Beneficial effect in mice	Ongoing clinical trial in human subjects	—
IgE and FcεRIα	Antibodies	No trials yet		
Syk	Fostamatinib (R788)	Phase II study in RA	No trials in SLE yet	82,83,84
Jak	CP690, 550 (Jak3 inhibitor)	Clinical trials in patients with psoriasis, RA, and kidney transplantation	No trials in SLE yet	—

ASPEN, Abetimus Sodium in Patients with a History of Lupus Nephritis; *BCMA*, B-cell maturation antigen; *BLISS*, study of Belimumab in Subjects with Systemic Lupus Erythematosus; *CTLA-4*, cytotoxic T lymphocyte–associated antigen; *IL-1Ra*, IL-1 receptor antagonist.

Findings of increased serum levels of IFN-α in patients with SLE and IFN signature in gene expression profiling of PBMCs from patients with SLE 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 patients with 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 the 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 I clinical trial suggest that a neutralizing mAb against IFN-α can ameliorate disease activity.[54]

Plasmapheresis (or plasma exchange) is a controversial treatment modality for patients with 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 patients with lupus nephritis. Several studies in the 1990s and an antibody rebound phenomenon was often noted after plasmapheresis. Plasmapheresis might 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

Intravenous immunoglobulin (IVIG) is a blood product prepared from plasma of multiple subjects. High-dose immunoglobulin has immunomodulatory properties. The exact mechanism of action of IVIG is not clear, although there are numerous proposed mechanisms of action of IVIG in patients with SLE. These are idiotypic network regulation, modulation of immune complex deposition, and complement regulation.[56] IVIG also suppresses the activation of B lymphocytes through enhancing expression of Fcγ receptor on B cells and DCs.[56,57] Interaction between

the Fc fragment of IgG and Fcγ receptor on target cells appears to be essential for many anti-inflammatory effects and in B cells. Cross-linking the BCR to the FcγRIIB is responsible for decreasing antibody production. There are no large randomized clinical trials looking at the efficacy of IVIG in patients with SLE. There are small clinical trials, case series, and case reports in the literature supporting its use in patients with SLE 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] and membranous or membranoproliferative lupus nephritis.[68] There is a pilot study showing temporary beneficial effects in patients with mildly to moderately active SLE.[69] There is no role for IVIG as a first-line treatment in patients with SLE, but it might 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 patients with 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, autoimmune diabetes, experimental arthritis, experimental uveitis, and 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_H subsets and, importantly, the T-cell immunoregulatory subsets.

It has been demonstrated that T cells that recognize an immunoglobulin 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 Fc region of IgG or with control plasmids. The conjugation of the peptide with the immunoglobulin Fc 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 the severity of nephritis.[71] Studies suggest that expression of the anti-DNA immunoglobulin consensus sequence induced immunoregulatory T cells and 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, IL-17, COX-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 TGF-β.[72] Statins seem to suppress IFN transduction pathways and IFN-γ–induced MHC class II expression in various cell types. Statin-induced repression of MHC class II also represses MHC class II–dependent activation of T cells. Statins also decrease the expression of costimulatory and adhesion molecules.[72]

Statins might also play an important role in the prevention of cardiovascular diseases in patients with SLE. In addition to their effects on the suppression of cholesterol synthesis, statins have a direct effect on endothelium, plaque formation, and thromboxane synthesis. Statins are also reported to have antithrombotic/anti-inflammatory effects in patients with antiphospholipid syndrome.[73] A recent controlled study (not placebo controlled) demonstrated a reduction in SLE disease activity after atorvastatin therapy in addition to an improvement in endothelial-dependent vasodilatation in patients with SLE after 8 weeks.[74] Another statin, simvastatin, also led to a similar reduction in disease activity in female patients.[75] A 1-year trial with atorvastatin demonstrated a decrease in cholesterol levels, proteinuria, and rate of progression of chronic kidney disease in patients with SLE with lupus nephritis.[76]

In another study there were no significant effects of fluvastatin on cardiac events in renal transplant recipients with SLE.[77] Thus we need multicenter and prospective studies to see whether and which statin treatment in patients with SLE is associated with a decrease in cardiovascular morbidity and mortality and has an effect on systemic and organ-specific inflammation.

Antioxidants: N-acetylcysteine and cysteamine

Antioxidants might 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 nonenzymatic antioxidants N-acetylcysteine and cysteamine on glomerulonephritis and mortality in the NZB/W F1 murine model of SLE, significant benefit was observed. N-acetylcysteine suppressed autoantibody formation and prolonged survival. Cysteamine inhibited the development of renal insufficiency and improved survival significantly.[78] Thus antioxidants might be a beneficial adjunctive therapy in the treatment of SLE and are being evaluated in an ongoing clinical trial.

Anti-IgE antibodies and Anti-FcεRIα antibodies

Human IgE molecules bind specifically and with very high affinity to receptors (FcεRI) on the surface of human basophils and mast cells. IgE autoantibodies are found in the sera of patients with autoimmune diseases, such as RA, SLE,[79] and systemic sclerosis,[80] and 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 of BAFF when activated by immune complexes containing IgE antibodies and therefore contribute to a loss of B-cell tolerance.

Thus the IgE-FcεRI network has potential to be a novel therapeutic target in patients with SLE. Moreover, cross-linking of FcεRI with FcγRIIb leads to inhibition of basophil degranulation,[81] suggesting another therapeutic target in patients with SLE, focusing on IgE antibodies.

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 in immune cells. Syk is overexpressed in T cells from patients with SLE. 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.[82] This drug has also been shown to prevent the 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.[83] Syk inhibition resulted in prompt clinical improvement in patients with RA in a phase II study.[84] It was also beneficial in patients with idiopathic thrombocytopenia.[85] Syk inhibition might be a valuable treatment for patients with SLE.

Janus kinase inhibition

The Janus kinases (Jaks) Jak1, Jak2, Jak3, and Tyk2 are a subgroup of the nonreceptor protein tyrosine kinases. They are involved in the 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 the innate and adaptive immune system. There are clinical trials with the Jak3 inhibitor CP690550 in patients with psoriasis, RA, and kidney transplantation. In a phase IIA randomized, double-blind, placebo-controlled study of patients with RA who had previously experienced failed therapy, CP690550 demonstrated an American College of Rheumatology 20/50/70 response of 80%/33% to 54%/13% to 28%, respectively. Dose-dependent neutropenia and anemia were observed. There are ongoing studies assessing the safety and efficacy of CP690550 compared with placebo in combination with methotrexate and in comparison with TNF blockade. R348, another Jak3 inhibitor, is in a phase I trial in patients with RA. It still needs to be determined whether Jak3 antagonists are acting on T cells, B cells, or both and, if T cells, on which subset. Jak3 is important for IL-21 signaling, but whether T_H17 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 the treatment of SLE, focusing on current approved therapies, ongoing clinical trials, treatment successes and failures, and novel approaches that have a potential to be used in the future, are discussed in detail (Table I). 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 the cascade of events promotes disease flare. The answers to these questions might lead to early diagnosis of SLE and early therapeutic intervention, which might increase the chances of remission and improve prognosis and quality of life, as well as life expectancy, in the long run. Biomarkers that will help us to identify SLE 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 divide patients into subsets with respect to genetic susceptibility, pathogenetic mechanisms, and phases of the 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 outcomes for patients 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 adaptive immune systems are dysregulated in patients with SLE.**
- **Antimalarial, anti-inflammatory, 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 patients with lupus with therapeutics having different mechanisms of action, such as classical immunosuppression, 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 might ultimately help identify at-risk subjects.**

What is still unknown?

- **Better and targeted therapies with fewer side effects are needed in the treatment of 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 might improve efficacy, as might combining BAFF blockade with B-cell depletion therapy.**
- **There are difficulties in division of patients into subsets, trial design, current disease activity measurement tools, and the proper use of combination therapies that might limit our ability to discern clinical benefit.**

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