Therapeutic modalities in systemic lupus erythematosus

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ABSTRACT

يعد مرض الذئبة الحمراء الشامل من أمراض المناعة الذاتية الشامل مع اختلافات مهمة طبية. كما أنه له العديد من المظاهر من إزالة ميالين الدماغ حتى تقشر الجلد. وهو من الأمراض المعقدة ويحتوي على مكونات جينية، وتقلبات الكريات اللمفاوية A و B، ووجود الأجسام المناعية والتي تشكل أساس الالتهاب وظهور المرض في أجهزة الجسم المختلفة. اشتملت الأدوية التقليدية للذئبة الحمراء على مضادات الالتهاب، ومضادات الملاريا، والسترويدات، والأجسام المناعية السامة مع التركيز على تطور العوامل الحيوية التي تمنع من الخلايا المناعية ذاتية الاستهداف ويقطع الإشارات الخلوية ويسهل تطور خلايا المنتظمة والتي تعد من الوسائل لعلاج هذه الأمراض. سوف تخوض هذه المراجعة أعراض المرض والأدوية الطبية المتوفرة حديثاً والعلاجات المتوفرة الأخرى مثل الذئبة الحمراء العصبية والنفسية وتسليط الضوء على أدوية المناعة والأدوية الحديثة التي تطورت لأعراض معينة مثل الأمراض العصبية، والنفسية، والجلدية.

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with significant clinical heterogeneity. Its pathogenesis is complex and involves multigenic components, dysregulation of T and B lymphocytes and the presence of autoantibodies, which form the basis for inflammation, and the pathology found in the various organ systems. Traditional treatments for SLE have included non-steroidal anti-inflammatory drugs, antimalarials, corticosteroids, and cytotoxic/immunosuppressants, but a recent emphasis on the development of biological agents that inhibit autoreactive B cells, interrupt cytokine signaling and facilitate the development of regulatory T cells has become a new modality in treating the disease. This review will delve into the pathogenesis of the disease process, as well as the current and up and coming novel biological treatment and other therapies for specific disease manifestations, such as neuropsychiatric SLE and cutaneous lupus erythematosus, and detail the shift to immune targeted therapies and novel treatments being developed for specific manifestations of the disease.

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From its early categorization as an "erythema group" disease under Dr. William Osler in the early 19th century to our more modern understanding of systemic lupus erythematosus (SLE) as a systemic autoimmune disease with symptoms ranging from cutaneous to visceral, our understanding of the disease, and therefore our treatment modalities have undergone many changes. Organs and tissues commonly affected include muscle and joints, the brain, and the peripheral nervous system, lungs, heart, kidneys, skin, serous membranes, and components of the blood. The disease itself is characterized by pathogenic autoantibody formation, immune complex deposition and end organ damage.[1] The mainstays of treatment for SLE include non-steroidal anti-inflammatory drugs (NSAIDs), antimalarials, and oral corticosteroids for patients with mild SLE, with the addition of immunosuppressive and cytotoxic agents (azathioprine, mycophenolate mofetil [MMF], Cyclophosphamide [CYC], cyclosporine, and methotrexate [MTX]) for patients with more severe forms of SLE. In the past decade, there have been significant advances in the knowledge of immunopathogenesis and target immunotherapy directed at SLE.

Pathogenesis. Patients suffer from a wide array of symptoms and have a variable prognosis that depends upon the severity and type of organ involvement. Although primarily immunological, the pathogenesis of the disease is influenced and modified by non-immune

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systems like the endocrine or clotting systems. There are formidable roles for both T and B cells in our understanding of SLE. Patients with active SLE have lower percentages of cluster of differentiation (CD)4+CD25+ T cells than healthy controls and those with active disease.[2] Production of interleukin (IL)-2 and transforming growth factor beta (TGF-β) is lower in SLE patients than in controls.[3] The β cells are responsible for autoantibody production and immune complex deposition that leads to tissue injury. The β cells also serve as antigen presenting cells, secrete proinflammatory and immunoregulatory cytokines, IL10, and regulate T cell activation, anergy, proliferation and the differentiation of T cells and follicular dendritic cells. The consensus of investigators was that β cells could be modulated using antigen-specific interventions or disrupting B and T cell interactions. We will discuss these pathogenetic interactions under therapy.[4,5] Genetic associations include other loci that are constitutive. Genetic major histocompatibility complex (MHC) II alleles are associated with certain autoantibody groups and inherited complement deficiencies develop variants of lupus with specific clinical characteristics. There are class II antigens and human leukocyte antigen (HLA)-D locus associations to other diseases as well. These include rheumatoid arthritis, multiple sclerosis, idiopathic thrombocytopenic purpura (ITP), and rheumatic fever; overlap syndromes such as Sjogren's, scleroderma, thyroiditis, and the inflammatory diseases of muscle.

Clinical. Fatigue is well recognized, and is the most common and often the most debilitating symptom of SLE; similar to a bout of influenza. A curious pattern of fatigue is described in SLE when compared to patients with other multisystem autoimmune diseases.[6] In SLE, fatigue decreased in the morning and increased in the evening in contrast to other conditions, such as scleroderma where the opposite is true. Weight loss is common in patients with lupus and worsened when there is malabsorption due to overlapping illnesses, such as CREST syndrome (calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, and telangiectasia), mixed connective tissue disease (MCTD), or scleroderma. The fever of lupus is usually low grade and rarely exceeds 39°C (102°F), unless patients are taking immunosuppressive drugs and have a concurrent infection. Although the disease is no cure, an effective treatment for SLE requires confirmation of the diagnosis and the accurate determination of both disease activity and severity. Eleven criteria have been designated by the American College of Rheumatology (ACR) for classification (**Table 1**).[7,8]

The presence of 4 or more criteria out of the 11 possible is mandatory for the appropriate classification of SLE. When used, these are of value in clinical practice, and are 96% sensitive and specific.[9] Disease activity may be measured with validated instruments, such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA)-SLEDAI, British Isles Lupus Assessment Group Scale (BILAG), European Consensus Lupus Activity Measure (ECLAM), or Systemic Lupus Activity Measure (SLAM).

The arthritis of SLE is a non-erosive, non-deforming, symmetric arthropathy. Multiple joints are involved, and 80-95% of them are tender, swollen, and effusive joints. The most frequently involved joints are the proximal interphalangeal, metacarpal phalangeal, wrists, and knees. The most frequent musculoskeletal x-ray changes are soft tissue swelling, acral sclerosis, and periarticular demineralization. Avascular necrosis is a particular source of joint pain in SLE patients, and should be a part of every differential diagnosis. It is a feature found in patients who are ingesting corticosteroids and those with phospholipid antibodies.[10] Avascular necrosis (AVN) is commonly found in the hips, carpal bones of the wrist, and heads of the humerus and the knees. Less commonly, the shafts of the long bones can be affected. Anywhere from 5-10% of patients with SLE can have AVN, and these findings are not always associated with steroid use. Myositis is present in 3-5% of SLE patients with creatine phosphokinase (CPK) greater than 1000,[11] but clinical features such as myalgias distinct from fibromyalgia can be found in as many as 50% of patients. The CPK is rarely elevated above 1000, but an electromyogram (EMG) can be very abnormal. Biopsy evidence of immune complex deposition is found in all kidneys of all patients with SLE, regardless of urine sediment. Both diffuse proliferative glomerulonephritis and progressive forms of focal proliferative nephritis have poorer prognoses than membranous and mesangial forms of the disease. A renal biopsy must be carried out to gauge the extent of disease and include 2 components: light microscopy and immunofluorescence. Serial renal biopsy has prognostic value and is recommended for the regulation of chemotherapy in some patients.[12] A biopsy with immunofluorescent analysis and electron microscopy is also recommended. An adequate number of glomeruli should be obtained for verifiable diagnosis. For most patients, renal function early in the course of the disease is normal despite abnormal urine sediment. If the activity of the disease progresses unchecked, these parameters change rapidly. When proteinuria is found

Table 1 - Updated American College of Rheumatology Diagnostic Criteria for systemic lupus erythematosus.[7,8]

Criterion	Definition
1. Malar rash	Fixed, flat or raised erythema over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging (older lesions may demonstrate atrophic scarring)
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Arthritis	Non-erosive arthritis involving 2 peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	A) Pleuritis: Convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion, or B) Pericarditis: Documented by electrocardiography (ECG) or rub or evidence of pericardial effusion
7. Renal disorder	A) Persistent proteinuria >0.5 g/day or >3+ if quantitation not performed, or B) Cellular casts: may be red blood cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	A) Seizures: In the absence of offending drugs or known metabolic derangements (for example, uremia, ketoacidosis, electrolyte imbalance), or B) Psychosis: In the absence of offending drugs or known metabolic derangements (for example, uremia, ketoacidosis, electrolyte imbalance)
9. Hematologic disorder	A) Hemolytic anemia: with reticulocytosis, or B) Leukopenia: <4000/mm^3 total on 2 occasions, or C) Lymphopenia: <1500/mm^3 on 2 occasions, or D) Thrombocytopenia: <100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder	A) Anti-deoxyribonucleic acid (DNA): antibody to native DNA in abnormal titer, or B) Anti-Smith (Sm): presence of antibody to Sm nuclear antigen, or C) Positive finding of antiphospholipid antibodies based on (1) an abnormal serum level of immunoglobulin (Ig)G or IgM anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method, or (3) a false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption tests
11. Antinuclear antibody (ANA)	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome
Systemic lupus erythematosus can be diagnosed if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation	

qualitatively by urine dipstick (one gm or greater), a 24-hour urine protein and a creatinine ratio should be obtained to quantify the amounts. Neuropsychiatric manifestations can be found in as many as 66% of patients with SLE.[13] The pathophysiology of this clinical manifestation is not widely understood; however, thrombosis and vasculitis are not responsible for the large number of neuropsychiatric manifestations observed. Central nervous system (CNS) manifestations include seizures, psychiatric illness, and disorders of the cranial nerves.[14] The frequency of organic CNS manifestations in SLE has been reported as between 35 and 75%.[15,16] The peripheral nervous system is involved in as many as 18% of patients. Seizures are found in 15-20% of SLE patients.[17] Grand-mal tonic-clonic seizures are most common, although other seizures, such as Jacksonian, psychomotor, and absence attacks, have all been reported. On rare occasions, patients with SLE can present with status epilepticus. Overt psychosis can occur in 12% of cases, as well as a variety of organic brain syndromes. Severe depression is common to lupus patients, and is thought to be a disease manifestation rather than reactive depression from chronic disease. Sleep disturbances are common in lupus and not usually related to depression. Steroid psychosis is common in lupus patients on high-dose steroids for long periods.[18] Peripheral nervous system disease is found in 3-18% of patients and is largely a sensory only, or combined sensorimotor neuropathy.[19] Guillain-Barre´ syndrome, mononeuropathy, or mononeuritis multiplex has also been reported.[20] The laboratory diagnosis of CNS disease in SLE is difficult. Spinal fluid pleocytosis and/or high spinal fluid protein levels are the only helpful indicators that CNS disease is present. The magnetic

resonance imaging (MRI) and position electron tomography (PET) scanning show the most promise for diagnosing disease of the brain. Use of the newer modalities, such as Tc-99-HMAAQ brain SPECT, may have better utility in the diagnosis of CNS SLE.[21] The most common cause of death in SLE is early onset cardiovascular disease (CVD). Risk factors for accelerated atherosclerotic CVD are under intense study.[22] The antioxidant capacity of normal high-density lipoproteins (HDL) is lost during inflammation, and the dysfunctional HDLs predispose to atherosclerosis. These dysfunctional HDLs are thought to be the single factor that increases the risk of developing subclinical atherosclerosis in SLE. Cardiac involvement is very common in SLE, and some 30-50% of patients suffer from some form of heart disease.[23,24] Pericarditis, the most common form of acute heart disease occurs in 19-48% of patients. Systolic cardiac murmurs are heard in up to 70% of SLE patients. These may be related to anemia, fever, or hypoxemia, and are found with Libman-Sacks endocarditis, a component more frequent with antiphospholipid antibodies. The mitral and aortic valves are involved most commonly. Pulmonary arterial hypertension is common in patients with phospholipid antibodies,[25] and a pulmonic murmur or a loud second heart sound in the presence of an elevated partial thromboplastin time (PTT) are clues to this diagnosis, which should be confirmed by echocardiography or cardiac angiography. Vasculitis is common in SLE and may be reflected in the presence of splinter hemorrhages, digital infarcts, or ecthymic skin lesions. Involvement of small- and medium-sized arteries may mimic polyarteritis nodosa and produce localized signs. The lungs are commonly affected in lupus patients.[26,27] Over 50% of SLE patients have some form of pleural disease and pleural effusions in their lifetime. These effusions are mostly exudative (>3 g protein), and less common than the pain and findings associated with simple pleuritis. Hemoptysis and overt pulmonary hemorrhage are emergencies in SLE patients and are either the result of pneumonitis or pulmonary embolus, which are reversible. There is also an association of alveolar hemorrhage with renal microangiopathy. Sixty to 80% of lupus patients have anemia of chronic disease. Other kinds of anemia, such as autoimmune hemolytic anemia, are rare and are found in less than 10% of patients; however, a positive Coombs test can be found in 20-60% of patients.[28] Leukopenia can be found in over 50% of patients with SLE and is associated with either granulocytopenia, or lymphopenia. Most low cell counts in SLE can be reversed with immunosuppressive therapy. Leukopenia is often a good general sign of disease exacerbation but also occurs in response to cytotoxic agents used in lupus therapy. Platelet transfusions are contraindicated in most SLE patients except on occasions where platelets reach dangerous levels, because of the possibility that patients will be exposed to new platelet antigens that make them more refractory. Anticlotting factor antibodies have been found in SLE and are often associated with bleeding. Antibodies are directed most commonly to factors II, VIII, IX, XI, or XII. Acquired von Willebrand syndrome is also seen. Lupus anticoagulants are found commonly in patients with SLE and are associated with mild to profoundly elevated partial thromboplastin times. This abnormality is usually associated with hyper coagulation and not with bleeding.[29] Associations have been observed, and the triad of the lupus anticoagulant, recurrent abortions, and the presence of false-positive tests for syphilis is often found in patients. Ninety percent of lupus patients have some involvement of the skin. Only 40% of patients experience sensitivity to ultraviolet (UV) light, and these are mostly Caucasians.[30] The actual percentage prevalence is 57% Caucasian versus 11% African-American. The lupus band test is the definitive test for cutaneous lupus. A biopsy shows immunoglobulin and complement deposition at the dermal epidermal junction in nonlesional skin in greater than 60% of patients with SLE.[31] Its true value is the differentiation of discoid lupus from SLE. In discoid lupus, only lesional skin stains positive, whereas in SLE, both lesional and nonlesional skin stain with immunoglobulin at the dermal epidermal junction. Chronic forms of lupus skin disease include several forms of discoid lupus and lupus profundus. These discoid lesions are usually localized to the head, scalp, and external ear, but more widespread involvement is possible. Patients with isolated discoid lupus have a 2-10% chance of developing systemic disease, whereas 10-20% of SLE patients have discoid lesions. Discoid LE is more common in African-Americans. Acute cutaneous lupus (30-50%) and subacute cutaneous lupus (10-15%) comprise the vast majority of patients with dermal disease. The butterfly malar rash found in 40% of patients is part of acute cutaneous lupus. Subacute cutaneous lupus (SCLE) is an annular, widespread, non-scarring or papulosquamous/psoriasis-form lesion that is worsened by sun exposure. This form of lupus is associated with HLA-DR3, anti- Ro antibody, and high titers of antinuclear antibody (ANA). The eye is not commonly involved in SLE. Only 10% or less of patients have episcleritis or conjunctivitis. In a prospective study, retinopathy was detected in 7% of SLE patients. This retinopathy consists of

microangiopathic lesions with cotton wool spots and hemorrhages that can be a significant problem in someone with a bleeding diathesis, or one who is anticoagulated. Optic neuritis, papilledema, and retinal vein occlusion are also major problems.[32] Lupus retinopathy is common in patients with active SLE (88%) and in those with lupus cerebritis (73%). Patients can also have uveitis, cytoid bodies, and angle-closure glaucoma. Patients with lupus may have vocal cord paralysis, or present with hoarseness because of vasculitis of the recurrent laryngeal nerve. Lupus may be a cause of sensorineural learning loss. The mechanism of ear damage is not known.

Therapies. The mainstays of treatment for SLE include NSAIDs, antimalarials, and oral corticosteroids for patients with mild SLE, with the addition of immunosuppressive and cytotoxic agents (azathioprine, mycophenolate mofetil, Cyclophosphamide, cyclosporine, and methotrexate) for patients with severe SLE. The NSAIDs are generally effective for arthritis, musculoskeletal complaints, fever, headaches, and mild serositis.[33] Naproxen may have greater relative cardiovascular safety than other NSAIDs.[34] The major side effects of NSAIDs include renal and hepatic impairments, gastrointestinal discomfort, bleeding, cardiovascular risk, and aseptic meningitis.[35,36] Antimalarials remain as a first-line treatment for patients with mild SLE along with NSAIDs. The mechanism of action of antimalarials in the treatment of SLE is not fully understood, but is believed to be due to their inhibition of phagosome function by increasing intracellular pH resulting in the disruption of class II major histocompatibility complex molecules, thereby inhibiting toll-like receptor (TLR) activation leading to a down-regulation of interferon-alpha (INF-α) and decreasing the antigen processing necessary for autoantigen presentation.[37] Antimalarials also decrease CD4+ T cell stimulation and the generation of proinflammatory cytokines, such as IL-1, IL-2, IL-6, and TNF-α.[38] Antimalarials are most useful for constitutional (fatigue, fever), musculoskeletal, skin, and mild pleuritic complaints.[39] Evidence has been shown that antimalarials help maintain remission, preventing major disease flares and major damage to the kidneys and central nervous systems, and reducing the required prednisone dose for patients with SLE.

A systemic review reported that antimalarials reduced lupus activity by more than 50% in pregnant and nonpregnant patients, and a greater than 50% improvement in mortality.[38] Antimalarials have also been shown to have mild antiplatelet and antithrombotic effects, and have possible thromboprotective effect in lupus patients with antiphospholipid syndrome. Hydroxychloroquine is the most commonly used antimalarials agent in the United States. It is relatively safe when used during pregnancy.[39] Corticosteroids rapidly reduce inflammation and immunomodulate the innate and adaptive immune systems, resulting in amelioration of SLE-related manifestations.[40] The dose of corticosteroids treatment in SLE depends on the severity and organ involvement of the disease. A low-dose of oral prednisone (0.1 to 0.2 mg/kg) may be used for mild SLE for treatment of cutaneous and musculoskeletal symptoms not responding to other therapies,[41] a median dose (0.5 mg/kg) may be considered for moderate SLE with pleuropericarditis or hematological involvement, and a high-dose of oral prednisone (1-1.5 mg/kg) or intravenous methylprednisolone (one g or 15 mg/kg) for 3 consecutive days is used for severe disease involvement (renal, CNS, systemic vasculitis). Treatment with cytotoxic/immunosuppressive agents is reserved for more severe manifestations of the disease; these include MTX, azathioprine, CYC, and MMF. Cyclosporine and leflunomide are less commonly used. Most data with these agents are in the area of SLE nephritis. All of these agents should be avoided during pregnancy. The MTX is an antifolate. It inhibits the enzyme aminoimidazole carboxamide ribonucleotide (AICAR) transformylase, leading to increased adenosine release, a potent anti-inflammatory/inhibitor of neutrophil function.[42] The MTX may be effective in patients who have articular or cutaneous involvement, allowing lower steroid doses, and slightly decreasing lupus disease activity. Azathioprine is a purine analogue that inhibits nucleic acid synthesis, and affects both cellular and humoral immune functions. It is effective in patients with SLE who have arthritis, serositis, and mucocutaneous manifestations. Azathioprine is also used frequently as a steroid-sparing agent, and it has proved to be effective in maintaining disease remission. The CYC is a synthetic antineoplastic agent. Its action involves interference with the transfer of alkyl groups, thereby interfering with cell growth (especially pre-B cells) and various cellular functions.[23] The CYC has long been the standard treatment for severe organ-threatening SLE, together with high-dose corticosteroids, for lupus nephritis, CNS lupus, and severe systemic vasculitis.

The most common dosing regimen follows the National Institutes of Health (NIH) protocol that includes monthly intravenously infusion of CYC (0.5-1.0 g/m^2 body surface area) for 6 months, and then once every 3 months for 2 more years.[23] In another protocol, the Euro-Lupus Nephritis Trial

protocol, CYC is given intravenously at 500 mg every 2 weeks for 3 months, followed by azathioprine, or the NIH regimen as a long-term maintenance therapy.[43] The MMF is a reversible inhibitor of the enzyme inosine monophosphate dehydrogenase, impairing purine (guanosine) synthesis. The MMF blocks the proliferation of activated T and B lymphocytes. In addition, depletion of guanosine nucleotides decreases the expression of adhesion molecules and reduces lymphocyte influx to inflammatory sites, such as the kidney.[44] The MMF is given at a dose of one to 3 g/day. The MMF in combination with corticosteroids was shown to be as effective as CYC in the treatment of lupus nephritis. Based upon pathogenetic mechanisms, there are B cell targeted therapies that have had significant success.[45] These agents include rituximab, ocrelizumab, belimumab, epratuzumab and atacicept. Rituximab (RTX) is a chimeric mouse/human monoclonal antibody specific for human CD20, a B cell surface antigen expressed only on mature B cells. Thus rituximab selectively depletes CD20+ mature B cells from the peripheral circulation but allows their regeneration from hematopoietic stem cells.

A number of open-label and retrospective studies have demonstrated the efficacy of RTX in the treatment of SLE patients who had failed to standard treatment. In addition, a large prospective data from the French Autoimmunity RTX registry reported response rates in articular (72%), cutaneous (70%), renal (74%), and hematologic improvement (88%) of the RTX-treated patients.[46] However, these promising results were not confirmed by 2 randomized multicenter controlled trials, the EXPLORER and LUNAR trials. Both studies failed to meet their primary or secondary end points in RTX-treated lupus patients, with or without renal involvement. An aggressive standard of care with high-dose corticosteroids and immunosuppressants may have masked the efficacy of RTX in the EXPLORER and LUNAR trials. In summary, the role of RTX in the treatment of SLE is still controversial. Currently, RTX is not an approved agent for the treatment of SLE. Nevertheless, in refractory SLE patients (especially in patients with cytopenia, nephritis, or neuropsychiatric lupus) the addition of RTX to the immunosuppressant (as an off-label drug) may be considered. Belimumab is a fully human, monoclonal antibody that binds to soluble B lymphocyte stimulator (BlyS, also known as the B-cell-activating factor), and selectively neutralizes BlyS without recognizing other tumor necrosis factor family members.[47] Intravenous belimumab is approved as add-on therapy in adults with active, antibody-positive SLE with high degree of disease activity despite standard therapy in Europe, United States and Canada. The initial dose of belimumab is given at 10 mg/kg at a 2 week interval for the first 3 doses, and then it is given at the same dose every 4 weeks.

The efficacy of belimumab was demonstrated by 2 large, multinational, randomized, double blind, phase III studies, BLISS-52 and BLISS-76 trials.[45,48] In seropositive patients with active SLE receiving standard therapy, SLE responder index (SRI) response rate at 52 weeks were significantly higher in patients receiving belimumab 10 mg/kg than those receiving placebo. The durability of the treatment effect of belimumab relative to placebo was not sustained at week in the BLISS-76 trial. In addition, Belimumab was associated with a significant reduction in SLE disease activity measured by SELENA-SLEDAI, PGA (patient general assessment) scores, no worsening of BILAG score and reduction in the risk of a serious flare.[45] The mean time to the first SLE flare was significantly increased in patients treated with belimumab compared to patients treated with placebo.[45] Ocrelizumab is a humanized anti CD20 antibody. The study of ocrelizumab in SLE was halted because of significant serious opportunistic infections. Epratuzumab is a humanized monoclonal antibody against CD22, an antigen involved in B cell signaling and Atacicept is another monoclonal antibody directed to a member of the TNF super family APRIL. Both agents are in phase II and III clinical trials as potential additions to the biological therapy of SLE.

Therapy for specific disease manifestations. Neuropsychiatric lupus. Neuropsychiatric SLE developed in 20-70% of SLE patients during the course of their disease.[16] The ACR identified 19 neuropsychiatric syndromes that are associated with SLE.[49] Cognitive dysfunction, mood disorder, and headache are the most common symptom out of 19 syndromes. Some investigators believe that anti-ribosomal P antibodies have been associated with lupus psychosis and depression,[50,51] and cognitive defects may be associated with the presence of elevated levels of antineuronal antibodies, antiphospholipid antibodies, or antibodies to N-methyl-D-aspartate (NMDA),[52-54] although other studies have not confirmed these.[55-57] There is limited data on specific treatment for neuropsychiatric SLE. Some neuropsychiatric SLE manifestations such as cognitive dysfunction are difficult to evaluate. Patients with neuropsychiatric involvement are excluded from most clinical trials of therapeutic agent because they cannot sign the informed consent. Treatments usually focus on the specific neuropsychiatric symptoms rather than on treating the lupus (for example, anticonvulsants to treat seizures or antidepressants for

patients with depression). Regular use of aspirin may help prevent cognitive decline, particularly in older patients. A beneficial effect of aspirin was seen in a prospective cohort study of 123 patients.[58] Psychosis due to (active) organic involvement by SLE usually responds to steroids. Treatment should be initiated with prednisone (one to 2 mg/kg per day) given for a few weeks, then a trial of cytotoxic therapy (for example, pulse cyclophosphamide) should be attempted if no improvement. Azathioprine may be an effective yet safer alternative to continued cyclophosphamide for long-term maintenance following recovery from an episode of psychosis.[59-62] Life-threatening neuropsychiatric manifestations such as myelitis, acute confusional state with coma may be managed with high-dose corticosteroids, plasmapheresis and other immunosuppressive agents (for example, MMF and CYC). Rituximab may be an alternative agent for patients with refractory disease.

Cutaneous lupus erythematosus (CLE). The CLE is a heterogeneous disorder with a wide range of skin manifestation. It is further divided by 4 subtype including acute CLE, subacute cutaneous lupus erythematosus (SCLE), discoid lupus erythematosus (DLE), and lupus erythematosus tumidus (LET). Treatment of CLE is focused to the subtype, the inflammatory activity and to the extent of skin lesions. Controlled randomized double blind studies for CLE are limited. In addition to strict photoprotection mentioned above, topical corticosteroids are an appropriate first-line therapy.[63,64] Topical calcineurin inhibitors, which lack the atrophogenic effects of corticosteroids, have also been shown to be effective for the treatment of DLE.[65,66] Intralesional corticosteroid injections can be used to treat patients with focal lesions that do not respond to topical treatment.[67] Systemic treatments should be considered for widespread skin lesions, rapidly progressive and highly inflammatory disease, and lack of response to topical therapy. Antimalarials (for example, Hydroxychloroquine) are drugs of first choice for all subtype.[68,69] The CLE patients who have failed topical, intralesional, and antimalarial therapy can be treated with MTX, systemic retinoids, MMF, or Dapsone.[68,70-74] Among these agents, MTX and retinoids have the strongest evidence for efficacy, although their use is limited in young women due to teratogenicity. For patients with refractory CLE who fail to above therapies, thalidomide or IVIG may be alternative options for inducing remission.[75-77] Patients treated with thalidomide should be well-informed of the potential adverse effects, including teratogenicity and polyneuropathy.

In conclusion, SLE is a heterogeneous disorder that can affect several organ systems. The treatment for SLE is generally individualized, based on clinical presentation of the patient. The goal of the treatment is to induce improvement and maintain it. Antimalarials and NSAIDs are the mainstay of treatment for mild SLE. Corticosteroids and cytotoxic/immunosuppressive agents should be used for SLE patient with severe, chronic and specific organ involvement. Belimumab has been approved as an add-on treatment for active and antibody positive SLE. There are other target immunotherapies in clinical trials and these hold the promise of effective treatment for SLE patients in the future. Other organ-specific manifestations may be treated with therapy targeting the specific conditions, such as antidepressant for SLE with depression.

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