SYSTEMIC LUPUS ERYTHEMATOSUS TREATMENT AND RECENT ADVANCES.

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Key Concepts  
- Definition of Systemic Lupus Erythematosus  
- Management of Systemic Lupus Erythematosus  
- Disease modifying of Systemic Lupus Erythematosus  
- Side effects of treatment of Systemic Lupus Erythematosus

Abstract: Systemic lupus erythematosus is a systemic autoimmune disease (or autoimmuneconnective tissue disease) that can affect any part of the body. The course of the disease is unpredictable, with periods of illness (called flares) alternating with remissions. Treatment of systemic lupus erythematosus (SLE) is guided by the individual patient's manifestations. B lymphocytes (B cells) are one of the immune cells responsible for the damage in autoimmune disease.

Key Words: SLE, Belimumab, Methotrexate, Immune globulin intravenous.

Introduction  
Systemic lupus erythematosus often abbreviated as SLE or lupus, is a systemic autoimmune disease (or autoimmuneconnective tissue disease) that can affect any part of the body. As occurs in other autoimmune diseases, the immune system attacks the body's cells and tissue, resulting in inflammation and tissue damage.¹ SLE most often harms the heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system. The course of the disease is unpredictable, with periods of illness (called flares) alternating with remissions. The disease occurs nine times more often in women than in men, especially in women in child-bearing years ages 15 to 35, and is also more common in those of non-European descent.²³⁴ Lupus is Latin for wolf. In the 18th century, when lupus was just starting to be recognized as a disease, it was thought that it was caused by the bite of a wolf.⁵ This may have been because of the distinctive rash characteristic of lupus. (Once full-blown, the round, disk-shaped rashes heal from the inside out, leaving a bite-like imprint.

Treatment  
Treatment of systemic lupus erythematosus (SLE) is guided by the individual patient's manifestations. Fever, rash, musculoskeletal manifestations, and serositis generally respond to treatment with hydroxychloroquine, nonsteroidal anti-inflammatory drugs (NSAIDS), and steroids in low to moderate doses, as necessary, for acute flares.
tions such as methotrexate may be useful in chronic lupus arthritis, and azathioprine and mycophenolate have been widely used in lupus of moderate severity.6

Central nervous system involvement and renal disease constitute more serious disease and often require high-dose steroids and other immunosuppressive agents, such as cyclophosphamide, azathioprine, or mycophenolate. Class IV diffuse proliferative lupus nephritis has also been treated with aggressive cyclophosphamide induction therapy.7,8

**Antimalarials**
Antimalarial agents may work through numerous proposed mechanisms in SLE, mediating subtle immunomodulation without causing overt immunosuppression. These drugs are useful in preventing and treating lupus skin rashes, constitutional symptoms, arthralgias, and arthritis; antimalarials also help to prevent lupus flares and have been associated with reduced morbidity and mortality in SLE patients followed in observational trials.9

**Hydroxychloroquine (Plaquinil)**
Hydroxychloroquine inhibits chemotaxis of eosinophils and locomotion of neutrophils and impairs complement-dependent antigen-antibody reactions. Hydroxychloroquine sulfate 200 mg is equivalent to 155 mg hydroxychloroquine base and 250 mg chloroquine phosphate. Weight-based dose adjustment and monitoring help to mitigate the risk of retinal toxicity.10

**NSAIDs**
NSAIDs are used to relieve pain and reduce signs of inflammation: fever, swelling and redness. People may take NSAIDs for temporary conditions such as sprains, strains, flares of back pain, headache and painful menstrual periods. NSAIDs also are a common treatment for chronic (long-term) health problems such as arthritis and lupus.

**Ibuprofen**
Ibuprofen is the drug of choice for patients with mild to moderate pain. It inhibits inflammatory reactions and pain by decreasing prostaglandin synthesis.

**Naproxen**
Naproxen is used for relief of mild to moderate pain. It inhibits inflammatory reactions and pain by decreasing activity of the enzyme cyclooxygenase, resulting in prostaglandin synthesis.

**Diclofenac**
Diclofenac inhibits prostaglandin synthesis by decreasing activity of enzyme cyclo-oxygenase, which in turn decreases formation of prostaglandin precursors.

**DMARDS, Immunomodulators**
Disease-modifying antirheumatic drugs (DMARDS) are immunomodulatory agents that act as immunosuppressives and cytotoxic and anti-inflammatory medications. The specific agent selection is generally indicated by the patient’s organ involvement and disease severity. Due to toxicity, cyclophosphamide is reserved for severe organ-threatening disease. At the other end of the spectrum, methotrexate or azathioprine may be helpful for milder arthritis or skin disease. DMARDS can be used in patients whose condition has had an inadequate response to glucocorticoids. Azathioprine, mycophenolate, and cyclosporine have all been studied for lupus manifestations such as nephritis.
Cyclophosphamide is used for immunosuppression in cases of serious SLE organ involvement, especially severe CNS involvement, vasculitis, and lupus nephritis. This agent is chemically related to nitrogen mustards. As an alkylating agent, the mechanism of action of the activemetabolites may involve cross-linking of DNA, which may interfere with growth of normal and neoplastic cells.

**Methotrexate**
Methotrexate is used for managing arthritis, serositis, cutaneous, and constitutional symptoms. It blocks purine synthesis and 5-aminomimidazole-4-carboxamideribonucleotide (AICAR), thus increasing anti-inflammatory adenosine concentration at sites of inflammation. Methotrexate ameliorates symptoms of inflammation and is particularly useful in arthritis treatment.

**Azathioprine**
Azathioprine is an immunosuppressant and a less toxic alternative to cyclophosphamide. It is used as a steroid-sparing agent in nonrenal disease. Azathioprine antagonizes purine metabolism and inhibits synthesis of DNA, RNA, and proteins. It may decrease proliferation of immune cells, which results in lower autoimmune activity.

**Mycophenolate**
Mycophenolate is useful for maintenance in lupus nephritis and other serious lupus cases. This agent inhibits inosine monophosphate dehydrogenase (IMPDH) and suppresses de novo purine synthesis by lymphocytes, thereby inhibiting their proliferation. Mycophenolate also inhibits antibody production.

**Immune globulin intravenous**
Intravenous immune globulin is used for immunosuppression in serious SLE flares. It neutralizes circulating myelin antibodies through anti-idiotypic antibodies. This agent downregulates proinflammatory cytokines, including interferon-gamma; blocks Fc receptors on macrophages; suppresses inducer T and B cells; and augments suppressor T cells. Immune globulin also blocks complement cascade, promotes remyelination, and may increase cerebrospinal fluid IgG (10%).

**Corticosteroids**
Corticosteroid agents are used predominantly for anti-inflammatory activity and as immunosuppressants. Preparations include oral, intravenous, topical, and intra-articular injections.

**Methylprednisolone**
Methylprednisolone is used for acute organ-threatening exacerbations. It decreases inflammation by suppressing migration of polymorphonuclear leukocytes and reversing increased capillary permeability.

**Prednisone**
Prednisone is an immunosuppressant for treatment of autoimmune disorders. It may decrease inflammation by reversing increased capillary permeability and suppressing polymorphonuclear neutrophil activity. Prednisone stabilizes lysosomal membranes and suppresses lymphocytes and antibody production. Low-dose oral prednisone can be used for milder SLE, but more severe involvement necessitates high doses of oral or intravenous therapy.

**Others**
**Rituximab (Rituxan)**
B-cell depletion with rituximab has been used successfully for rheumatoid arthritis, but it has shown mixed results for the treatment of SLE. One open study using rituximab
reported excellent results as rescue therapy for patients with active SLE who were unresponsive to standard immunosuppressant therapy.\textsuperscript{11} However, 2 large placebo-controlled studies failed to show an overall significant response.\textsuperscript{13,12} Note that rituximab has an off-label indication for SLE.

**Recent advances**

**Belimumab**

Belimumab (trade name Benlysta, previously known as LymphoStat-B) is a human monoclonal antibody that inhibits B-cell activating factor (BAFF),\textsuperscript{14} also known as B-lymphocyte stimulator (BLyS).\textsuperscript{15} B cells are responsible for part of the normal immune response, and also for the over-aggressive immune response in autoimmune diseases like systemic lupus erythematosus (SLE).

Belimumab is approved in the United States, Canada and Europe for treatment of SLE. However, the major phase III trials excluded the more severe cases of SLE with kidney and brain damage, so its effectiveness has not been demonstrated in those cases. A Phase III study for SLE patients with kidney disease is now recruiting.\textsuperscript{16}

U.S. F.D.A. reviewers were concerned that belimumab is only “marginally” effective, and that there were more deaths in the treatment group. Belimumab’s defenders said that in addition to its modest efficiency, belimumab allowed patients to significantly reduce their use of corticosteroids.\textsuperscript{17}

**Uses**

While belimumab appears safe in systemic lupus erythematosus, the magnitude of benefit is small.\textsuperscript{18} Black/African American patients did not show a benefit. The most severe cases, with kidney and central nervous system involvement, were excluded from the trials.

The efficacy and safety of belimumab was demonstrated in 2 Phase III randomized, controlled studies, BLISS-52\textsuperscript{19} and BLISS-76.\textsuperscript{20} The 2 studies had a total of 1,684 patients, with scores of $\geq 6$ on the SELENA-SLEDAI assessment. They were divided into a placebo and 2 dosage groups of belimumab, in addition to standard therapy. The primary end point was a reduction of $\geq 4$ on the SELENA-SLEDAI assessment, and several other factors, at 52 weeks. Belimumab significantly improved the response rate, reduced disease activity and severe flares, and was well tolerated. 58% had SELENA-SLEDAI scores reduced by $\geq 4$ points during 52 weeks with belimumab 10 mg/kg compared to 46% with placebo.

Benlysta was the first new drug to treat lupus after 56 years. Sales rose to $31.2 million in the first quarter of 2012.\textsuperscript{21} It is marketed by GlaxoSmithKline and sold for about US$35,000 per year per patient.

**Mechanism of action**

B lymphocytes (B cells) are one of the immune cells responsible for the damage in autoimmune disease. B cells develop in the bone marrow and continue to mature peripherally in secondary lymphoid organs and (as recently discovered) in the gut. When autoimmune B cells attack the body’s own tissues, they are normally destroyed by cell suicide (apoptosis). In order to survive, B cells need survival factors. Researchers theorize that SLE is caused when autoimmune B cells proliferate, and survival factors protect them from cell suicide.

B-cell activating factor (BAFF), also called
B-lymphocyte stimulator (BLyS), is required for the development and survival of B cells. In SLE, BAFF is overexpressed. Researchers theorize that BAFF overexpression causes autoimmune B cell proliferation and survival, which causes SLE.

Belimumab is a human antibody that binds to BAFF, preventing BAFF from binding to B cells. Without the survival factor BAFF, B cells commit suicide, and no longer contribute to the autoimmune damage of SLE.

BAFF is secreted by a variety of cells: monocytic and macrophage cells, bone marrowstromal cells, astrocytes, synoviocytes during rheumatoid arthritis, salivary epithelial cells during Sjögren’s syndrome, astrocytes in certain glioblastomas.

BAFF interacts with three membrane receptors on B lymphocytes:
- BAFF-R (BAFF receptor)
- BCMA (B cell maturation antigen)
- TACI (transmembrane activator and calcium modulator and cyclophylin ligand interactor)

When BAFF binds to BAFF-R and BCMA on B cells, levels of Bcl-2, a survival factor, are increased.

When all three BAFF receptors are stimulated, levels of NF kappa B, which contributes to cell proliferation and differentiation, are increased in the nucleus.

Another B-cell activator like BAFF is APRIL (a proliferation-inducing ligand), but APRIL only activates BCMA and TACI, not BAFF-R.

Belimumab reduces the number of circulating B cells, but anti-CD20 monoclonal antibodies reduce the number even more. It is possible that belimumab binds primarily to circulating soluble BAFF, therefore not inducing antibody-dependent cellular cytotoxicity that could be expected from this IgG1-type antibody.

**Side effects**

Common adverse effects reported with belimumab include nausea, diarrhea, fever, as well as hypersensitivity and infusion-site reactions (severe in 0.9% of patients). It is suggested that patients be treated with an antihistamine prior to a belimumab infusion.

A greater number of serious infections and deaths were reported in patients treated with belimumab than in those treated with placebo. Infections are due to the immunosuppressant properties of the drug.

**Interactions**

No interaction studies have been carried out. Combination of belimumab with other immunosuppressants, especially those targeting B lymphocytes such as anti-CD20 therapies, could increase the risk of severe infections. Likewise, the combination with cyclophosphamide is not recommended, as well as administering live vaccines during treatment with belimumab.

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