Systemic lupus recent advances in management

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Abstract: Systemic lupus erythematosus (SLE) is chronic inflammatory multisystem disorder of uncertain etiology. Diagnosis and management of SLE is challenging as it involves multiple organs has various presentations. Diagnosis of SLE has been standardized based on various professional organizations. Newer therapies using immunosuppressive therapies & monoclonal antibodies are discussed.

Key words: SLE, B cell activating factor (B A F F), ACR criterion, ANA, SLEDAI, Belimumab, Epratuzumab

Systemic lupus erythematosus is a chronic inflammatory multisystem disorder of unknown cause that can affect the skin, joints, kidneys, lungs, nervous system, serous membranes, and/or other organs of the body. Immunologic abnormalities, especially the production of a number of antinuclear antibodies, are another prominent feature of the disease. The clinical course of disease is punctuated by periods of remissions and of chronic or acute relapses. Prognosis is quite variable and depends upon the severity and type of organ involved and is occasionally life threatening.

EPIDEMIOLOGY:
Incidence of SLE varies depending of sex, age, race and ethnicity. Prevalence ranges from 10 to 400 per 1 lac population(1). It usually presents in individual in their twenties or thirties. Age group of presentation varies with ethnicity as shown by occurrence of disease in younger population in India when compared to North American population(2). Females are 10 times more frequently involved than men. Highest prevalence of disease is seen in black women when compared to white men(3).

ETIOPATHOGENESIS: The exact etiology of the disease is not yet clearly defined but was probably thought due to a complex interplay between genetic, environmental, immunologic factors and hormonal factors

GENETIC FACTORS: Genome-wide association studies have identified approximately 50 gene loci with polymorphisms that predispose to SLE. Genetic information accounts for only 18 percent of susceptibility to SLE, suggesting a large component of environmental or epigenetic influences.

- The most common genetic predisposition is found at MHC locus and specially the HLA-DR2 and HLA-DR3, with a hazard ratio of 2.
- Genetic factors that confer the highest HR of 5 to 25, though rare, are deficiencies of the complement components C1q (required to clear apoptotic cells), C4A and B, C2, or the presence of a mutated TREX1 gene.
Genetic predisposing variants involve some associated with innate immunity (IRF5, STAT4, IRAK1, TNFAIP3, SPP1, and TLR7), most of which are associated with interferon alpha pathways. Still other predisposing genes involve lymphocyte signaling (PTPN22, OX40L, PD-1, BANK-1, LYN, BLK), each of which plays a role in activation or suppression of T cell or B cell activation or survival.

In addition to genes, epigenetic modifications are important in pathogenesis of SLE. These include hypomethylation of DNA, which influences transcription into protein.

ENVIRONMENTAL FACTORS:
- Viruses stimulate specific cells in this immune system and antibodies to these molecular mimicry molecules may contribute to the development of autoimmunity. In addition, trypanosomiasis or mycobacterial infections may induce anti-DNA antibodies or even lupus-like symptoms, and lupus flares may follow bacterial infections.
- UV light may stimulate keratinocytes to express more snRNPs and to secrete more IL-1, IL-3, IL-6, GM-CSF and TNF-alpha, thereby stimulating B cells to make more antibodies.

HORMONAL FACTORS: evidence of the immunoregulatory function of estradiol, testosterone, progesterone, dehydroepiandrosterone, and pituitary hormones, including prolactin, has supported the hypothesis that they modulate the incidence and severity of SLE.
- The use of estrogen-containing OCP is associated with a 50 percent increase in risk of developing SLE while either early onset of menarche (age ≤10 years) or administration of estrogen to postmenopausal women doubles their risk.
- Breastfeeding may decrease risk of developing SLE. Nulliparous women are at higher risk of SLE than are women who have given birth at least once.
- Treatment of women with clinically stable SLE with OCP for one year does not increase disease flares. However, treatment of postmenopausal women with hormone replacement may increase flares, although evidence is mixed.
- Hyperprolactinemia and hyperprogesteronemia are associated with flares of SLE.

IMMUNE ABNORMALITIES: SLE is primarily a disease with abnormalities in immune regulation. There are numerous immune defects in patients with SLE. However, the etiology of these abnormalities remains unclear; we do not know which defects are primary, and which are secondarily induced. These abnormalities are thought to be secondary to a loss of self tolerance; thus, affected patients consequently develop an autoimmune response.
- B cells/plasma cells that make autoantibodies are more persistently activated and driven to maturation by B cell activating factor (BAFF, also known as B lymphocyte stimulator, blys) and by persistently activated T helper cells making B-supporting cytokines such as IL-6 and IL-10. Blys is essential for maturation and survival of post-bone marrow transitional and immature B cells into autoantibody-secreting plasmablasts and memory B cells.
- Antibody-Antigen complexes, particularly those containing DNA or RNA/proteins, activate the innate immune system via TLR9 or TLR7, respectively. Thus, dendritic cells are activated and release type 1 interferons and TNF-alpha, T cells release IFN-gamma, IL6, IL10, while
natural killer (NK) and T cells fail to release adequate quantities of transforming growth factor (TGF)-beta. These cytokine patterns favor continued autoantibody formation.

- Phagocytosis and clearing of immune complexes, of apoptotic cells, and of necrotic cell-derived material are defective in SLE, allowing persistence of antigen and immune complexes. Immune complex may be present for years before the first symptom of disease appears.
- Blys production is promoted by increased TLR activation and increased type 1 and 2 interferon’s; in turn, blys promotes increased TLR activation. This contributes to sustained autoantibody production. Blys increases survival of B2 cells after their transitional T1 phase which bypass several deleting and anergizing tolerance mechanisms.

Whatever be the etiology all these factors result in formation of immune complexes which gets deposited in multiple organ systems of the body. Clinical manifestations depend on the organ that is involved.

CLINICAL MANIFESTATIONS:

- Most of the early manifestations of SLE are constitutional and non-specific which include fever, fatigue, weight changes. Some of the patients may be asymptomatic and present with features of specific organ involvement.
- Symptoms that stem from specific organ involvement include arthritis, cutaneous manifestations like malar and discoid rash, hematologic manifestations like anemia, thrombocytopenia with rash and recurrent infections due to leucopenia.
- Lung involvement can result in variable presentations which include Pleurisy, pleural effusion, pneumonitis, interstitial lung disease, pulmonary hypertension, and alveolar hemorrhage can all occur in SLE. The risk of thromboembolic involvement is increased in those with antiphospholipid antibodies or with lupus anticoagulant.
- Renal involvement is mostly sub clinical and is diagnosed by urine analysis which shows proteinuria and casts. Several forms of glomerulonephritis can occur, and renal biopsy is useful to define the type and extent of renal involvement.
- Neuropsychiatric manifestations and ocular manifestations are also commonly seen.

DIAGNOSIS: The diagnosis of SLE is straightforward in a patient who presents with several compatible clinical features and who has supportive laboratory studies. Several diagnostic criteria have been in clinical use but most clinicians rely of the ACR criteria\(^4\). Using these criteria patients can be classified as –
ACR criteria have some inherent weaknesses. As an example, one can have a renal biopsy demonstrating lupus nephritis, but the patient still fails to fulfill criteria. In an effort to address these weaknesses, a consensus group of experts on SLE, the Systemic Lupus International Collaborating Clinics (SLICC), has proposed revised criteria for SLE, the SLICC criteria. The SLICC criteria had greater sensitivity but lower specificity than the ACR classification criteria. These criteria were developed as classification criteria, which are most applicable to use for clinical and epidemiologic research. They have not been evaluated for use in diagnosis.
Classification as having SLE by the SLICC criteria requires either that a patient satisfy at least 4 of 17 criteria, including at least 1 of the 11 clinical criteria and one of the six immunologic criteria, or that the patient has biopsy-proven nephritis compatible with SLE in the presence of ANA or anti-dsDNA antibodies.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Acute cutaneous lupus</td>
<td>Malar rash</td>
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<tr>
<td>Chronic cutaneous lupus</td>
<td>Discoid rash</td>
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<tr>
<td>Non scarring alopecia</td>
<td>Diffuse thinning or hair fragility with visible broken hairs</td>
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<tr>
<td>Oral ulcers or nasal ulcers</td>
<td>Palate, buccal, tongue, OR nasal ulcers</td>
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<tr>
<td>Joint disease</td>
<td>Synovitis/ Tenderness involving 2 or more joints</td>
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<tr>
<td>Serositis</td>
<td>pleural effusions, pericardial effusions</td>
</tr>
<tr>
<td>Renal</td>
<td>Persistent proteinuria greater than 0.5 grams per day or Cellular casts.</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Seizures or psychosis.</td>
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<tr>
<td>Hemolytic anemia</td>
<td>Hemolytic anemia - with reticulocytosis.</td>
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<tr>
<td>Leukopenia/ lymphopenia</td>
<td>Leukopenia - less than 4000/mm total on two or more occasions or Lymphopenia - less than 1500/mm on two or more occasions.</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Thrombocytopenia - less than 100,000/mm.</td>
</tr>
<tr>
<td>ANA</td>
<td>An abnormal titer of Ana.</td>
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<tr>
<td>Anti ds DNA</td>
<td>Anti-dsDNA level above twofold the reference range if tested by ELISA.</td>
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<tr>
<td>Anti-sm</td>
<td>Presence of antibody to Sm nuclear antigen</td>
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<tr>
<td>Antiphospholipid antibody</td>
<td>Positive apa antibody.</td>
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<tr>
<td>Low complement</td>
<td>Low C3; low C4; OR low CH50</td>
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<tr>
<td>Direct coombs test</td>
<td>Direct Coombs’ test in the absence of hemolytic anemia</td>
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TREATMENT:

- There is no cure for SLE and complete remissions are rare.
- The presence of severe organ dysfunction does not necessarily imply ongoing inflammation. The ability to differentiate between these two possibilities is extremely important, since immunosuppressive therapy is indicated only in the latter setting.
- Flares are generally qualified by severity, with moderate or severe flares being the most clinically significant as these are once require that require aggressive management.
- An effective therapeutic regimen requires accurate determination of both disease activity and severity. There is no consensus on what constitutes a disease flare, but most definitions have incorporated a combination of results from serologic measures and disease activity indices.

Serological tests include:

- A raising titer of IgG anti-dsDNA titer
- Low levels of ch50, c3, c4
- Elevated ESR and CRP
- Low levels of c1q

A number of indices have been developed based on combination of history, examination and laboratory data. These include:

- Systemic Lupus Erythematosus (SLE) Disease Activity Index (SLEDAI),
- Safety of Estrogens in Lupus Erythematosus: National Assessment-SLEDAl (SELENASLEDAI),
- Systemic Lupus Activity Measure (SLAM),
- British Isles Lupus Assessment Group (BILAG),
- European Consensus Lupus Activity Measurement (ECLAM) and others.
HOW TO TREAT??

Treatment can be broadly divided into 2 categories:

- General non medical measures.
- Organ specific medical management.

ORGAN SPECIFIC MEDICAL MANAGEMENT: A number of medications are commonly used in the treatment of SLE including NSAIDs, antimalarials, glucocorticoids, and immunosuppressive agents.

NSAIDs: Topical therapies are often useful for cutaneous manifestations of lupus and reduce side effects associated with systemic use of NSAIDs. NSAIDs are generally effective for musculoskeletal complaints, fever, headaches, and mild serositis. Naproxen may have greater relative cardiovascular safety than other NSAIDs.

ANTIMALARIALS: Antimalarials are most useful for skin manifestations and for musculoskeletal complaints. In addition, in long-term studies, the use of antimalarials, such as hydroxychloroquine, prevented major damage to the kidneys and central nervous system\(^\text{6}\). Their use may also reduce the risk of disease flares, though this is less clear for renal and CNS manifestations.

GLUCOCORTICOIDS:

- Systemic steroids are the main stay in management of SLE.
- Glucocorticoids used alone or in combination with immunosuppressive agents are generally reserved for patients with significant organ involvement, particularly renal and CNS disease.
- Glucocorticoids appear to act in part by inducing the synthesis of IkBa, a protein that traps and thereby inactivates nuclear factor kappa B. The latter protein is an activator of cytokine genes and a mediator of the proinflammatory action of tumor necrosis factor. Pulse glucocorticoid administration may impair cytokine generation.
Usual way of inducing disease remission is by giving 1000 mg I.V methylpred for three successive days following by oral prednisone 40 mg-60 mg daily for 4 to 6 weeks. Thereafter doses are tapered as rapidly as clinical scenario permits to a maintenance dose of 5 to 10 mg daily\(^7\).

**IMMUNOSUPPRESSANT:** These are generally reserved for patients with significant organ involvement and/or for patients who have had an inadequate response to glucocorticoids. These include methotrexate, cyclophosphamide, azathioprine, mycophenolate.

- In patients in grade iii or iv renal disease, early treatment with glucocorticoids and cyclophosphamide/mycophenolate reduces progression to end stage renal disease.
- Marrow suppression, infections, hemorrhagic cystitis, alopecia, GI symptoms ovarian and testicular failure and malignancy are amongst the side effects of cyclophosphamide. These side effects are less common with IV regimen.
- Though mycophenolate is less toxic to cyclophosphamide, marrow suppression, infections, alopecia, cough, GI symptoms and malignancies are most commonly seen with mycophenolate with diarrhea being the most common side effect.
- Therapeutic response of cyclophosphamide and mycophenolate starts within 3-16 wks while that of steroids may begin within 24 hrs.
- For maintenance, mycophenolate may be better to azathioprine in preventing flares and progression to lupus nephritis, either drug is acceptable and both are safe compared to cyclophosphamide.
- The usual practice is to induce with 500-750mg/m\(^2\) iv cyclophosphamide, monthly for 6 month followed by maintenance with either mycophenolate(1-2gm daily) or azathioprine(2 mg/kg/day). European studies showed 500mg iv cyclophosphamide every 2 weeks for 6 doses is as effective as high dose regimen but with decreased side effects.

**NEW ERA OF BIOLOGICS:** At a time when it seemed that all rheumatoid arthritis trials were successful, a string of negative clinical trial results instilled profound skepticism in the SLE community on the feasibility of even doing such trials. Many trials were done but none were approved.

- In terms of impact, rituximab needs a special mention. Thought used as an off label medication for SLE two 2 large randomized controlled trials, THE EXPLORER and THE LUNAR failed short of approval.
- At a time when the hopes of ever seeing a successful clinical trial in SLE were fading and the lupus community was about to give up, the positive results of the BLISS-52 and BLISS-76 clinical trials saved the day.
- The approval of belimumab opened new gates of research for the role of biologics in SLE.
**BELIMUMAB**: This is the first FDA approved biologic after 50 yrs. It acts by inhibiting the biological activity of protein BLyS which is essential for B cell maturation, proliferation and survival and hence the antibody production.

**ADVANTAGES:**
- There is no drug interaction b/n belimumab and other drugs commonly used for SLE, and can therefore be added to patient's regular treatment.
- It increases disease free period and allows for reduction of steroid dose.

**INDICATIONS:**
- Used in patients with active SLE but without active renal or neurologic disease
- In non responders to steroids, HCQ and one immunosuppressant
- In patients who cannot receive these agents due to side effects

**DOSE:**
- 10mg/kg IV Q2weeks for 1st 3 doses and once every month thereafter

**SIDE EFFECTS:**
- Most common include nausea, vomiting, diarrhea and upper respiratory infections.

**RITUXIMAB**: Rituximab is a monoclonal antibody directed against the CD20 antigen on B-lymphocytes. It changes the immune system activity and prevents immune damage to vital organs including kidney.

**INDICATIONS:**
- Currently used as off label in treatment of lupus resistant to standard treatment.

**DOSE:**
- 375mg/m² once weekly for 4 weeks given as infusion with the first run over 5 and ½ hrs while rest at 4 and ½ hrs.
- Prior administration of anti-histamines, paracetmol and steroids will help to curtail infusion related reactions.

**SIDE EFFECTS:**
- Upper respiratory tract infections, low blood counts and low blood pressure are amongst the common side effects.
- Infusion related reactions include hypertension, headache, fever, chills and diarrhea.
**INTRAVENOUS IMMUNOGLOBULINS:** Its exact mechanism of action is not yet clearly defined but several suggested mechanism include suppression of WBC, inhibition of immune system activation and neutralizing antibodies that damage organs.

**INDICATIONS:**
- Used to treat variety of manifestations of SLE like anemia, thrombocytopenia, serositis, carditis, nephritis, encephalitis, and psychosis

**LATEST TREATMENTS OF CLINICAL SIGNIFICANCE:**

**LENALIDOMIDE:** Is a thalidomide derivative that inhibits the production of tnf α, interleukins and cell surface adhesion molecules. In addition it increases apoptosis by increasing NK cell number and function.

**INDICATIONS:**
- Safe and efficacious in refractory cutaneous lupus

**DOSE:**
- Started at 5 mg/day for 4 weeks and if no clinical improvement was observed, dose was increased to 10 mg/day. Otherwise, sustained at 5 mg/day in case of partial response or decreased progressively monthly in case of adequate response

**SIDE EFFECTS:**
- Notably common are insomnia, neutropenia and GI symptoms like nausea, vomiting and diarrhea.

**DRUGS IN TRIAL PHASE:**

**EPRATUZUMAB:** The anti-cd22 agent is believed to down regulate b-cells without depleting them. Doses of 600mg weekly show clinically significant improvement in moderate and severe lupus

**COSTIMULATORY MOLECULE TARGETS:** This group includes abatacept, a fusion protein of CTLA4 and Fc domain of human igg1 which is designed to block the interaction of CD80/CD86 on APC with CD28 on naive T cells.

**CYTOKINE TARGETS:** Sifalimumab and Rontalizumab act by neutralizing the type 1 INF gene expression in the blood and skin. Given the role of type 1 INF in the disease, several trials of anti-INF monoclonal antibody have been initiated\(^9\). Another of this kind, tocilizumab, anti-IL-6 receptor therapy showed promise in a phase 1 trial

**TOLEROGEN-TARGETING AGENTS:** Lupuzor, the spliceosomal peptide, can induce IL-10 production by CD4 T cells which in turn decreased levels of anti-dsDNA titers. Laquinimod, CNS active immunomodulator works by shifting immune modulation towards Th2 and suppress immune activation\(^10\).
References


