

Systemic Lupus Erythematosus (SLE)

Disease Overview

- Autoimmune disease that affects multisystem¹
- 1.5 million cases of lupus²
- Prevalence of 17 to 48 per 100,000 population³
- Women > Men - 9:1 ratio¹
- 90% cases are women²
- African Americans > Whites¹
- Onset usually between ages of 15 and 45 years, but can occur in childhood or later in life¹

¹U.S. Department of Health and Human Services. National Institutes of Health. National Institute of Arthritis and Musculoskeletal and Skin Diseases. NIH Publication No. 03-4178. August 2003.

²Lupus Foundation of America. Statistics About Lupus. Available at: <http://www.lupus.org/education/stats.htm>. Accessed February 13, 2006.

³Werth, VP. Clinical manifestations of cutaneous lupus erythematosus. Autoimmunity Reviews 4 (2005) 296-302.

Pathogenesis

- Etiology is unknown
- SLE is an autoimmune disease
- Genetic factors
 - HLA association
- Environment factors
 - Sunlight, drugs, chemicals, foods
 - Bacterial or viral infections
 - More associated with flares and exacerbations
- Hormonal factors
 - Increased estrogen and prolactin levels

Drug-Induced Lupus

- **Definitive:¹**
 - Procainamide
 - Hydralazine
 - Isoniazid
- **Others:²**
 - Chlorpromazine
 - D-penicillamine
 - Methyldopa
 - Quinidine
 - Ethosuximide

¹Kasper, DL, et al. *Harrison's Principle's of Internal Medicine*, 16th edition. Chapter 300. 2005.

²Kauffman MD, CL. Lupus Erythematosus, Drug Induced. 2006. Available at: www.emedicine.com. Accessed February 13, 2006.

Common Signs & Symptoms of Lupus

- Painful or swollen joints and muscle pain
- Unexplained fever
- Red rashes, most commonly on the face
- Chest pain upon deep breathing
- Unusual loss of hair
- Raynaud's phenomenon
- Sensitivity to the sun
- Edema in legs or around eyes
- Mouth ulcers
- Swollen glands
- Extreme fatigue

U.S. Department of Health and Human Services. National Institutes of Health. National Institute of Arthritis and Musculoskeletal and Skin Diseases. NIH Publication No. 03-4178. August 2003.

Diagnostic Criteria

- 4 of the following must be present:
 - Malar rash
 - Discoid rash
 - Photosensitivity to sun light
 - Oral lesions
 - 2 or more swollen joints-similar to RA
 - Pleuritis or pericarditis by ECG
 - Renal disorders
 - Neurologic disorders
 - seizure, psychosis, paralysis

Diagnosis

- **No single test can determine whether a person has lupus, but several laboratory tests may help make a diagnosis**
- **Diagnostic Tests**
 - **Antinuclear antibody (ANA) test**
 - **Autoantibodies: anti-DNA, anti-Sm, anti-RNP, anti-Ro (SSA), and anti-La (SSB)**
 - **Anticardiolipin antibody**
 - **Antiphospholipid antibody**
 - **Skin biopsy**
 - **Kidney biopsy**

Monitoring Disease Progression

- **Laboratory tests**
 - **Complete blood count (CBC)**
 - **Urinalysis**
 - **Blood chemistries**
 - **Erythrocyte sedimentation rate (ESR)**
 - **Complement levels**
 - **X-rays and imaging tests of affected organs**

Proactive and Preventive Strategies in SLE

- **Proactive**
 - Patient education programs
 - Eliminate patient nonadherence
 - Specialist access
 - Exercise, PT, OT, ergonomic work stations
 - Cognitive therapy (lupus fog), biofeedback (Raynaud's)
- **Preventive**
 - Aggressive vigilance for hypertension, hyperglycemia, hyperlipidemia, obesity, smoking cessation
 - Yearly bone densitometry and use of bisphosphonates
 - Annual EKG, chest X-ray, duplex scanning, stress tests, 2-D echo for pulmonary pressures in high-risk patients
 - Prompt evaluation of all fevers
 - Antiphospholipid antibody screening and prophylaxis

Treatment

- **Treatment plans are based on patient age, sex, health symptoms, and lifestyle**
- **Goals of treatment:**
 - **To prevent flares**
 - **To treat flares when they occur**
 - **To minimize organ damage and complications**

Current Therapies

- **NSAIDs**
 - To control pain, swelling, and fever
- **Antimalarials**
 - Generally to treat fatigue joint pain, skin rashes, and inflammation of the lungs
 - Commonly used: Hydroxychloroquine
 - Used alone or in combination with other drugs
- **Corticosteroids (Mainstay of SLE treatment)**
 - To rapidly suppress inflammation
 - Commonly used: prednisone, hydrocortisone, methylprednisolone, and dexamethasone
- **Immunosuppressives**
 - To block the production of immune cells
 - Used in patients whose kidneys or central nervous system has been affected
 - Commonly used: cyclophosphamide and mycophenolate mofetil

Other Therapies

- **Methotrexate**
- **Alternative and Complementary Therapies:**
No research to date shows that they alter the disease process or prevent organ damage, but may have symptomatic or psychosocial benefits
 - **Special diets**
 - **Nutritional supplements**
 - **Fish oils**
 - **Ointments and creams**
 - **Chiropractic treatment**
 - **Homeopathy**

New pathogenesis concepts since 2000

- **Pro-inflammatory HDL plays a role in atherogenesis**
- **Interferon signature specific for active SLE**
- **Defective apoptotic clearance—stimulates PDC—via TLR 7,8,9 (innate immunity) inside the cell triggered by self nucleic acids**
- **Heparin acts as an anti-inflammatory agent in APS in addition to its anticoagulant properties**

New drug development in SLE

Background

- No new drugs approved for SLE since 1966
- An FDA Guidance Document provides a roadmap for industry
- 7 factors are considered critical for approval; not all are needed

FDA Guidance Document (provisional)

- **Mandatory: the drug is safe**
- Improves 2 clinical indices; preferably the BILAG and either SLEDAI, SLAM or ECLAM
- A validated response measure shows amelioration (eg, RIFLE)
- SLICC/ACR damage index is slowed
- Quality of life (eg, SF-36) betterment
- Organ-specific improvement (eg, renal)
- Subpart H: biomarker/surrogate markers improve

Targets for New Therapies in SLE

- T cells
 - CTLA4 Ig; modified CD40L mAb
- B cells, anti-dsDNA antibodies
 - LJP 394; mAbs to CD20, CD22
 - antiBLyS, TACI-Ig, BAFF-RFc
- Complement
 - anti C5a
- Cytokines
 - mAbs to Type 1 IFN R
 - mAbs to IL-10, sIL-6R, IL-6
- Promote regulatory cells
 - Expand CD4+CD25+ cells,
 - CD8+CD28- cells
- Inhibition of interferon, toll receptors
 - anti-IFN-alpha, inhibit TLR 7-9
- T cell regulation of autoantibody production
 - Peptides derived from nucleosomes, Sm Ag, Igs, Edratide