Systemic Lupus Erythematosus Overview

Clinical presentation, pathophysiology, and therapeutic strategies over the course of disease

the upus initiative
Eliminating Health Disparities in Lupus

Eliminating health disparities • Cultura[illegible]ence • Genetic and non-genetic
• Genetic and non-genetic factors • [illegible]ty • Signs and symptoms of dise
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Renal • Cultural competence • Genetic and non-genetic factors • Health equity •
• Signs and symptoms of disease onset • Cardiovascular • Reproductive • Rena

Systemic Lupus Erythematosus (SLE)

- An inflammatory, multisystem, autoimmune disease of unknown etiology with protean clinical and laboratory manifestations and a variable course and prognosis
- Lupus can be a mild disease, a severe and life-threatening illness, or anything in between

Clinical Manifestations of SLE—Important Concepts

- The diversity of clinical symptoms in SLE is great, and all organ systems are vulnerable
- Different ethnic backgrounds are associated with differences in disease prevalence and severity
- Disease is characterized by periods of flare and remission and can culminate in irreversible end-organ damage

Video of Dr. Graciela Alarcón

The University of Alabama at Birmingham

Introduction

- Epidemiology
- Diagnosis
- Pathogenesis
- Mortality
- Therapeutic principles

Epidemiology

- **Prevalence:** 2–140/100,000 worldwide but as high as 207/100,000
- **Incidence:** 1–10/100,000 worldwide
- **Population at highest risk:**
  - Women in their reproductive years
  - Female:male ratio is approximately 9:1 postpuberty and premenopausal
- **Variation in race/ethnicity:** More common in Black (3−6x), Hispanic and Native American (2–3x), and Asian (2x) populations
- **Cost:** There are direct costs associated with treatment (eg, $100 billion in healthcare cost associated with autoimmune diseases) and indirect cost related to lost productivity and wages

Video of Dr. Graciela Alarcón

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ACR (Revised) Criteria for Classification 4/11= 95% Specificity; 85% Sensitivity

- **Malar rash**
- **Discoid rash**
- **Photosensitivity**
- **Oral ulcers**
- **Arthritis**
- **Serositis**
- **Glomerulonephritis**
- **Neurologic disorder:** Seizures and/or psychosis
- **Hematologic disorder:** Immune-mediated hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia
- **Antinuclear antibodies (ANA)**
- **Immunologic disorder:** anti-DNA antibody, anti-Sm antibody, or antiphospholipid antibodies

Tan EM, Cohen AS, Fries JF, et al. *Arthritis Rheum.* 1982;25:1271-1277. Hochberg MC. *Arthritis Rheum.* 1997;40:1725. [Letter].

Lupus on the Outside

Synovitis

Malar rash

Oral ulcer

Subacute cutaneous lupus erythematosus

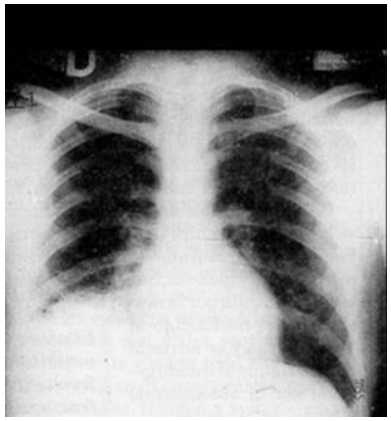
Discoid rash

Jaccoud's arthropathy

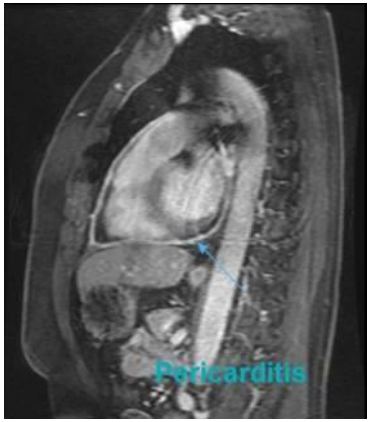
Vasculitis

Lupus profundus

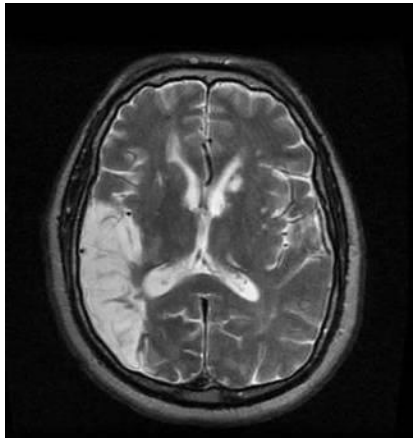
Lupus on the Inside



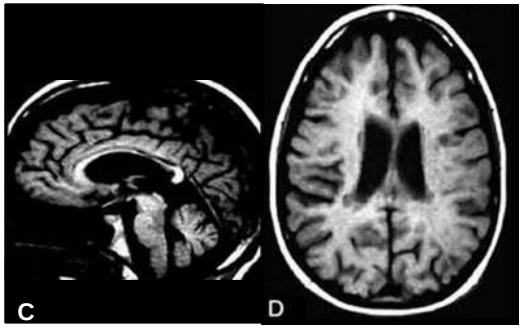
Serositis



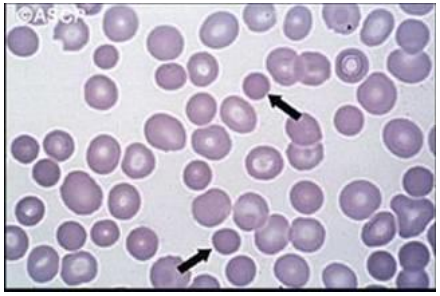
Pericardial effusion



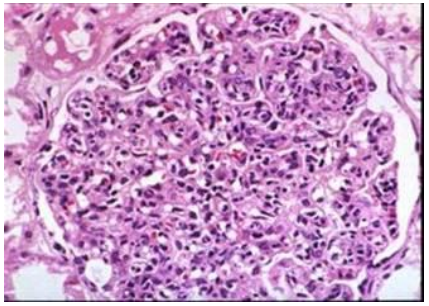
Cerebral infarct



Brain atrophy



Spherocytes



Glomerulonephritis

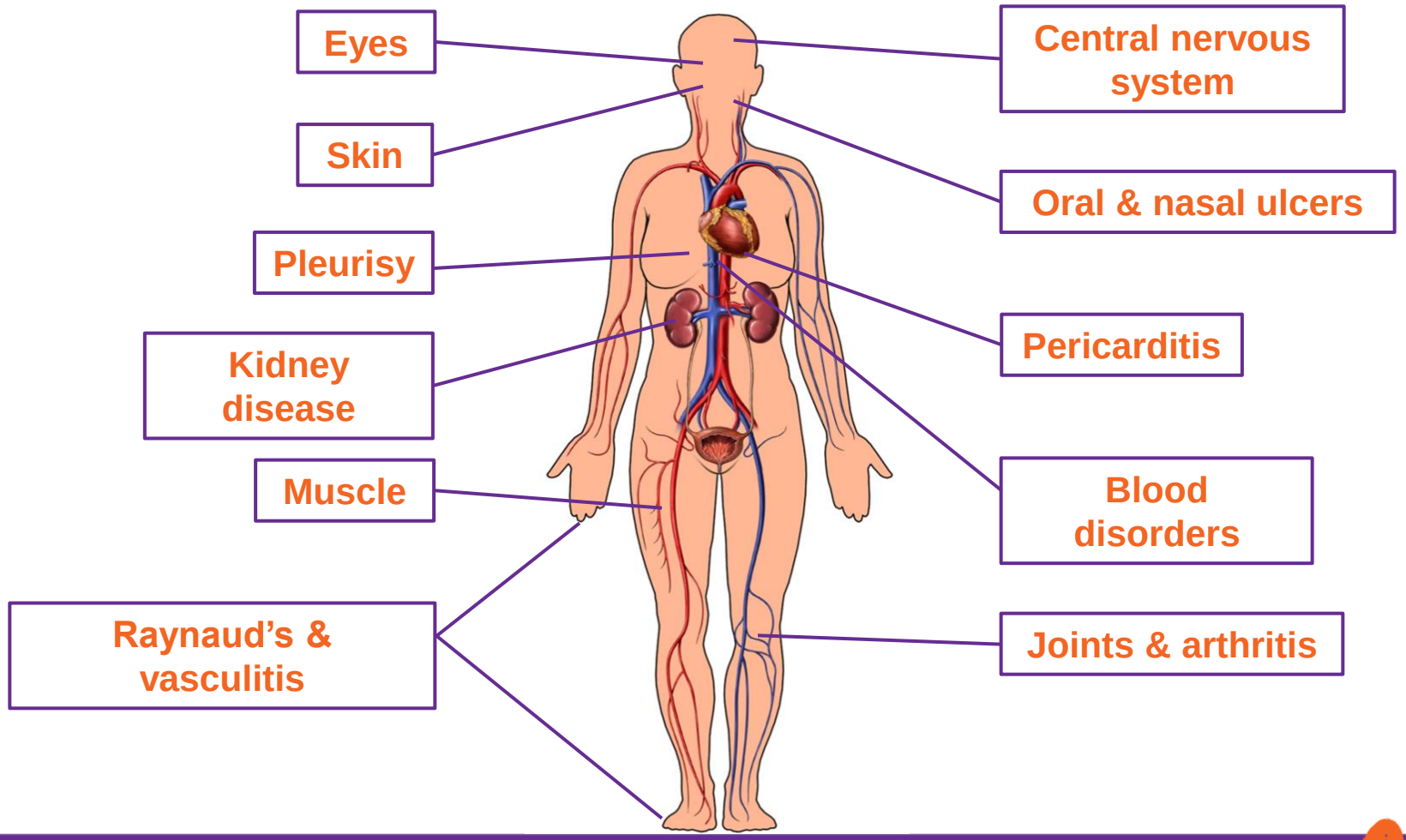
Lupus Intangibles

Fatigue

Memory thief

Depression

Examples of Organs Involved, Signs, and Symptoms



Case Presentation

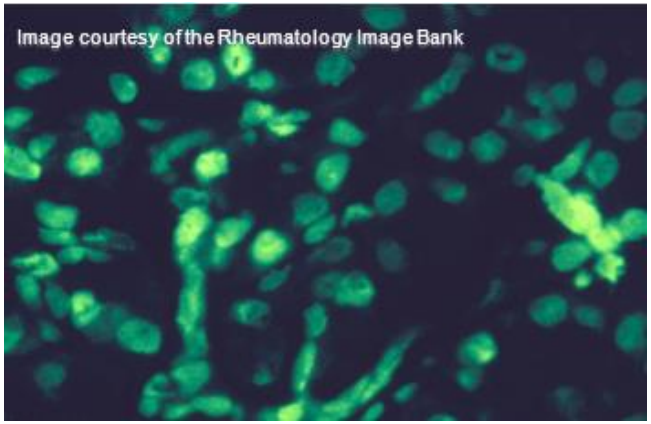
- **History:** A 23-year-old Hispanic female with no past medical history presented to the emergency department (ED) with an 8-week history of joint pain and swelling in the hands, knees, and ankles; fever; myalgias; pleuritic chest pain; weight loss; and a facial rash that worsened with sun exposure. She had been seen initially at a local clinic and treated for “cellulitis” with oral Keflex. Two days prior to this presentation, she was seen in another ED, found to have a temperature of 103 °F, proteinuria, and anemia; she was told it was a “viral syndrome” and discharged home

Case Presentation (cont.)

- **Exam:** T 37.9 °C, BP 130/90, painless ulceration on the palate, erythematous malar rash, diffuse lymphadenopathy, and synovitis of the MCP/PIP joints
- **Labs:** WBC 2.5x10^9/L, total protein 9 g/dL, albumin 3 g/dL, Hgb 11g/dL, Hct 32%, BUN 11 mg/dL, Cr .06 mg/dL
  UA: 100 mg/dL protein, RBC 20–40/hpf, WBC 0–1/hpf
  ANA+, anti-dsDNA+, Sm+

What Do All Lupus Patients Have in Common—Antinuclear Antibodies (ANA)

- Multiple methods for detection but immunofluorescence (IF) is the most reliable
- In an IF ANA assay, a serum sample is applied to a glass slide covered with fixed cells (to allow access to nuclear antigens)
- The antigen-antibody reaction is revealed by fluorochrome conjugated antihuman immunoglobulin antibodies
- The slide is then examined by fluorescence microscope



ANA present in 95%–98% of SLE patients

ANA

- Autoantibodies against various components of the cell nucleus
- Present in many autoimmune disorders as well as some healthy subjects
- Sensitive (not specific for SLE)

ANA (cont.)

- Because of low specificity, ANA usefulness increases if the pretest probability for lupus is high; ie, the patient has symptoms and signs that can be attributed to SLE
- Because of the high sensitivity of the ANA, a patient with negative ANA is unlikely to have lupus even when her/his clinical presentation is suggestive of lupus

Incidence of Positive ANA

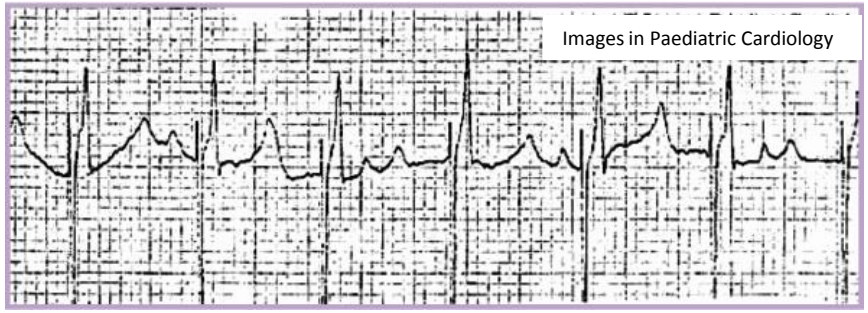
- Normal subjects 3%−4%
- SLE 95%−99%
- Scleroderma 95%
- Hashimoto's thyroiditis 50%
- Idiopathic pulmonary fibrosis 50%
- Incidence increases with age, chronic infections, and other chronic conditions

Pathogenic Autoantibodies—Anti-SSA and Anti-SSB

Subacute cutaneous lupus

Neonatal lupus

Complete heart block *in utero*

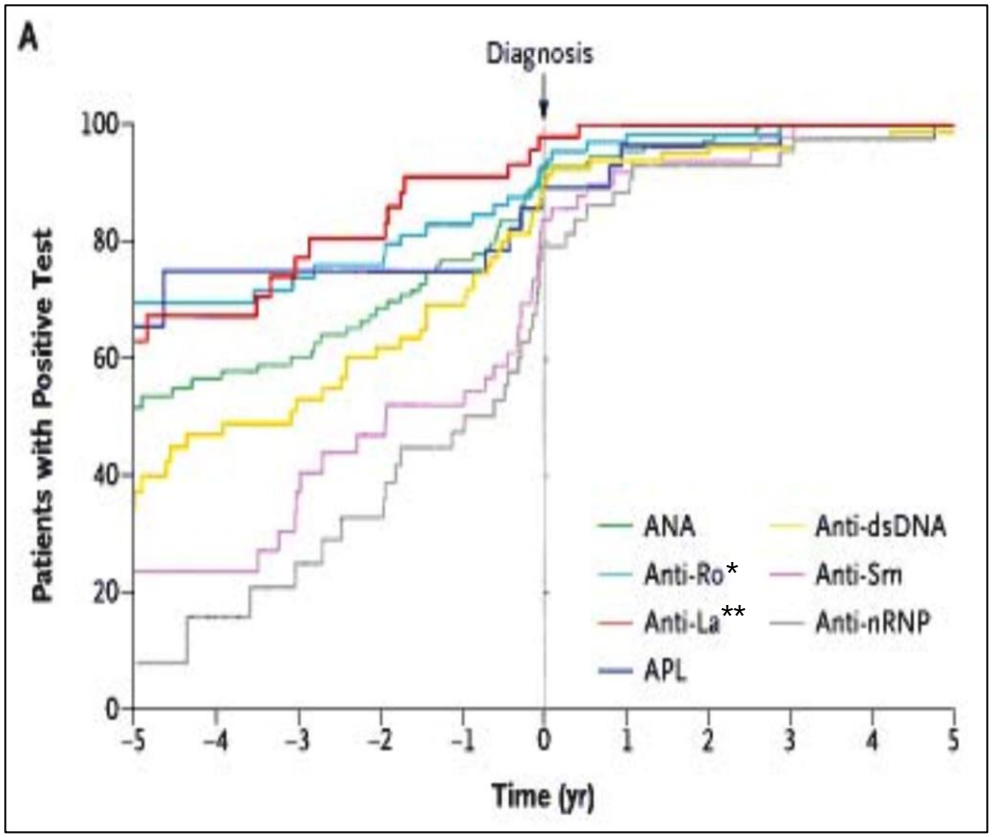


Autoantibodies in SLE

Antibodies	Lupus Specificity	Clinical Associations
ANA	Low	Nonspecific
Anti-dsDNA	High	Nephritis
Anti-Sm	High	Nonspecific
Anti-RNP	Low	Arthritis, myositis, lung disease
Anti-SSA	Low	Dry eyes/mouth, subacute cutaneous lupus erythematosus (SCLE), neonatal lupus, photosensitivity
Anti-SSB	Low	Same as above
Antiphospholipid	Intermediate	Clotting diathesis

Autoantibodies—Preclinical Detection

- Autoantibodies precede diagnosis by many years
- We are currently not able to predict which subjects with positive autoantibody titers will develop disease



*Anti-Ro = Anti-SSA
**Anti-La = Anti-SSB

Arbuckle MR, McClain MT, Rubertone MV, et al. *N Engl J Med*. 2003;349:1526-1533.

Phases of Disease Pathogenesis

- **Initiation**
  - Multiple proposed mechanisms that may vary from patient to patient
  - Occurs years prior to onset of clinical symptoms
- **Amplification and perpetuation** of dysregulated immune mechanisms and response of target organs to inflammatory insults
- **Irreversible damage** from disease and secondary effects of treatment

Genetic Susceptibility—Clinical Studies

- Rate of SLE concordance in monozygotic twins is 24%–35%; in dizygotic twins is 2%–5%
- 10%–12% of SLE patients have 1st- or 2nd-degree relatives with SLE compared with <1% in healthy individuals
- SLE patients may have family members with other autoimmune diseases

Sestak AL, Fürnrohr BG, Harley JB, et al. *Ann Rheum Dis.* 2011;70(suppl 1):i37-43. doi: 10.1136/ard.2010.138057.

Video of Dr. Lindsey Criswell

University of California, San Francisco
School of Medicine

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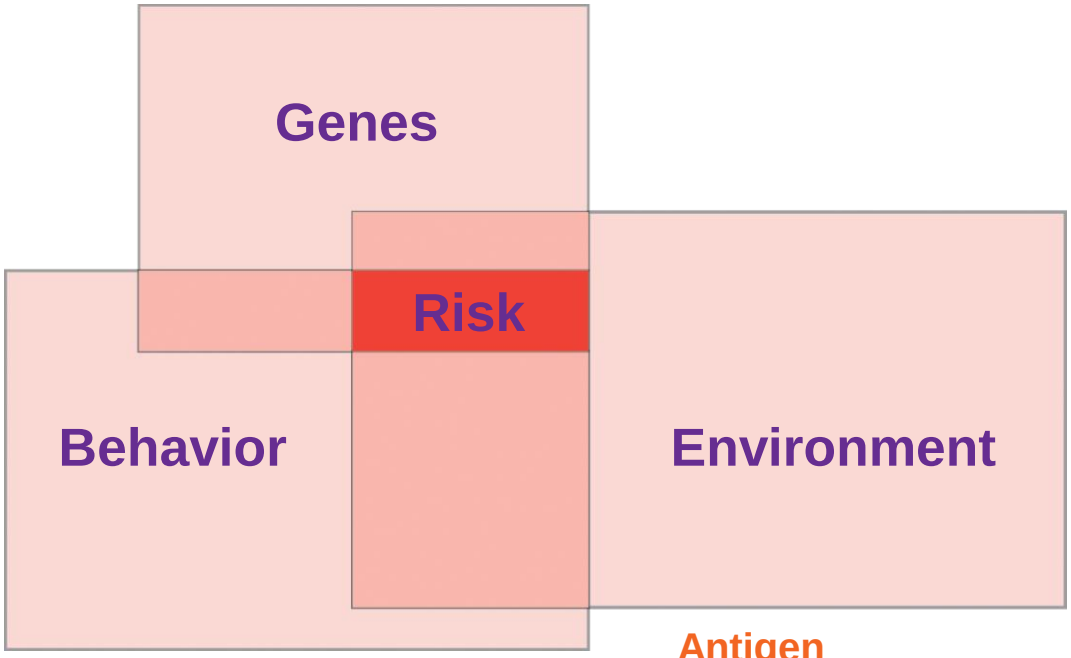
Causes of Autoimmune Disease Are Multifactorial



Smoking
Sun exposure
Stress
Toxins

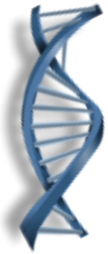
Antigen
Hormones (estrogen)
Infections
Toxins
Medications
Sun exposure
Vitamin D deficiency

SLE

Initiation

Amplification

Perpetuation



Genetic alterations

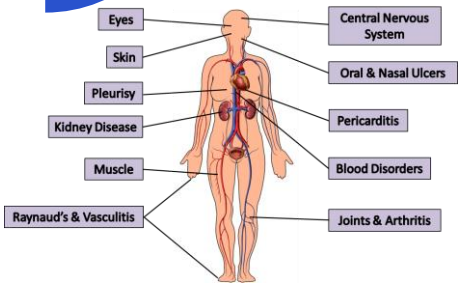
Environmental exposures

Abnormally functioning
B-cells
T-cells
pDC

Autoantibodies
ICs

Proinflammatory
molecules

TISSUE INJURY



Examples of Immune Dysregulation in Lupus

- **B-cells**
  - Defective selection/signaling
  - Autoantibody production
- **T-cells**
  - Increased numbers of Th17 and Th2 cells and decreased numbers of Tregs
  - T-cells are less susceptible to activation-induced cell death
- **Plasmacytoid dendritic cells**
  - Produce large amounts of interferon
  - Plasmacytoid dendritic cells: Stimulate activation and proliferation of autoreactive T- and B-cells

Pathogenesis of Lupus—Important Concepts

- Autoimmunity is an altered immune homeostasis that leads to autoreactivity, immunodeficiency, and malignancy
- Immune dysregulation leading to autoreactivity and autoantibodies in SLE occurs in different phases and likely represents the untoward effects of environmental triggers on the genetically susceptible host

Disease Activity

- SLE is characterized by periods of flare (increased disease activity) and remission or low-level disease activity
- Varying flare rates
- Predictors of flare (in some but not all cases)
  - New evidence of complement consumption
  - Rising anti-dsDNA titers
  - Increased ESR
  - New lymphopenia

Disease Severity

- Characterized by
  - Abrupt onset of symptoms
  - Increased renal, neurologic, hematologic, and serosal involvement
  - Rapid accrual of damage (irreversible organ injury)
- Associated with
  - Race/ethnicity (Black, Hispanic, Asian, and Native American populations)
  - Younger age of onset
  - Male gender
  - Lower socioeconomic status

Mortality

- 5-year survival rate in 1953 was 50%; currently >90%
- Leading causes of mortality are heart disease, malignancy, and infection
- Factors contributing to increased mortality*
  - Disease duration; increased mortality early on
  - High disease severity at diagnosis
  - Younger age at diagnosis
  - Ethnicity: Black, Hispanic, Asian, and Native American populations are at greater risk
  - Male gender
  - Low socioeconomic status
  - Poor patient adherence*
  - Inadequate patient support system*
  - Limited patient education*

*Indicates opportunity for improvement.

Bernatsky S, Boivin JF, Joseph L, et al. *Arthritis Rheum.* 2006;54:2550-2557.

Therapeutic Principles—Important Concepts

- Goals of therapy
  - Stop and reverse ongoing organ inflammation
  - Prevent or limit irreversible end-organ damage
- Potential toxicities of immunosuppressive therapies demand vigilant management
- Strategic use of targeted immunobiologic therapies based on pathogenic mechanisms vs global immunosuppression

Current Therapy for SLE

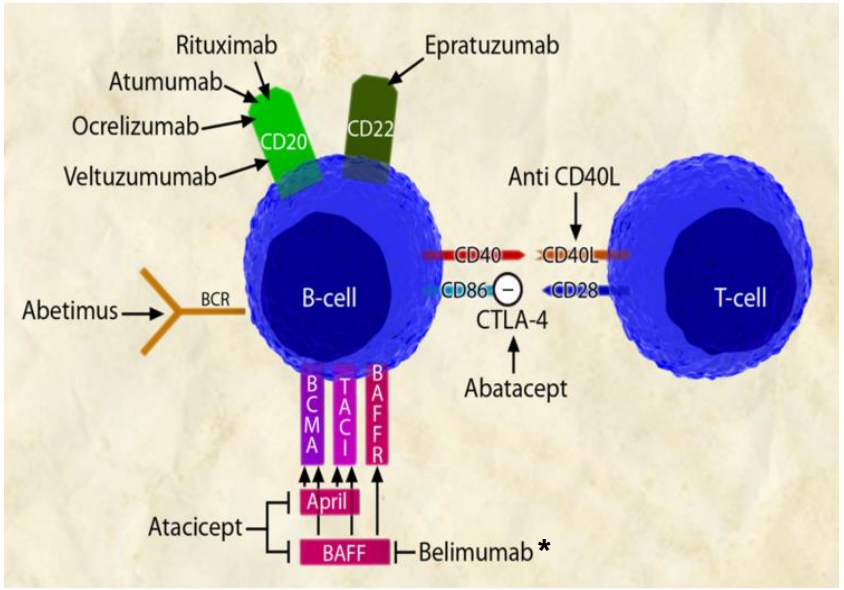
- Corticosteroids
- Cyclophosphamide
- Methotrexate
- Mycophenolate mofetil
- Azathioprine
- Hydroxychloroquine
- Belimumab

Current Therapy—Limitations

- Immunosuppressive drugs confer an increased risk for
  - Infection
  - Cancer
  - Infertility
- Common side effects of corticosteroids
  - Infections
  - Cushingoid appearance
  - Osteoporosis
  - Osteonecrosis
  - Diabetes
  - Mood disturbances
  - Hypertension
  - Lipid abnormalities

New Therapeutic Strategies—Targeted Immunotherapy

- Immune targeted therapy
  - B-cell directed
  - Cytokine inhibitors
  - Costimulation blockade
  - Peptide inhibitors
  - Kinase inhibitors
  - T regulatory cells
- Stem cell transplant



*Recently FDA approved for lupus

Yildirim-Toruner C, Diamond B. *J Allergy Clin Immunol.* 2011;127:303-312.

Guiding Therapeutic Strategies

- Therapeutic combinations aimed at **induction of remission**, **maintenance therapy**, and **supportive therapy**
- Titrate dose to treat effectively with focus on involved organs, and to minimize toxicity
- Strategic use of preventive therapies, antibiotics, and vaccinations
- Cardiovascular screening
- Cancer screening
- Osteoporosis screening

Lupus—In Summary

- Clinical disease is characterized by
  - Symptom diversity
  - Periods of flare and remission
- Pathogenesis is related to
  - Genetic susceptibility combined with environmental and/or behavioral triggers
  - Immune dysregulation characterized by autoantibody production
- Treatment is targeted to
  - Clinical manifestations
  - Severity of organ system involvement

Bibliography

Slide 10 References
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