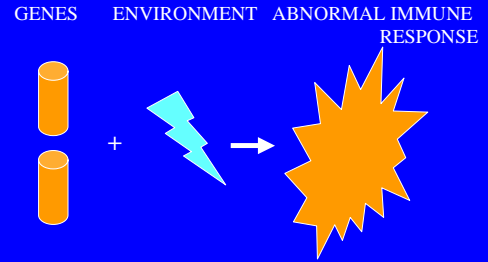


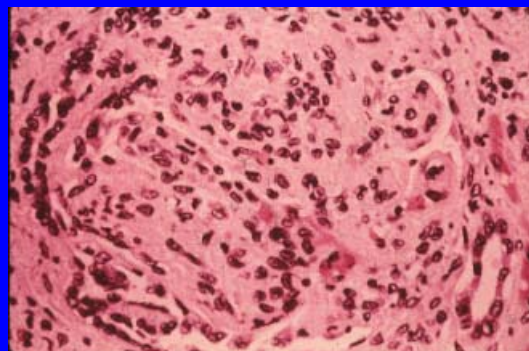
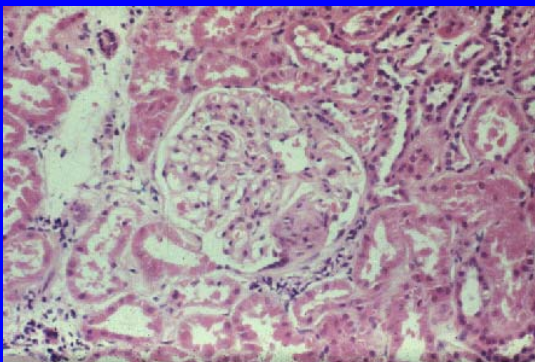
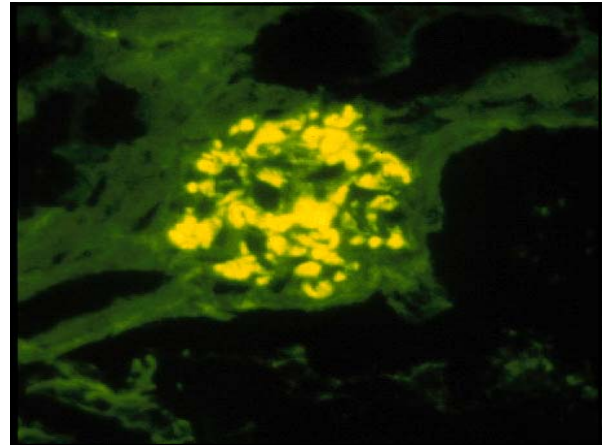
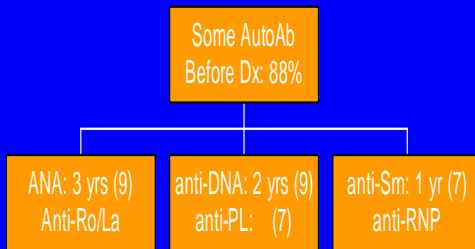
Systemic Lupus Erythematosus

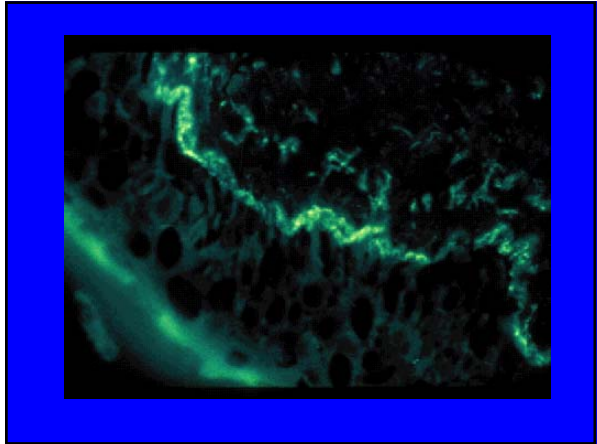
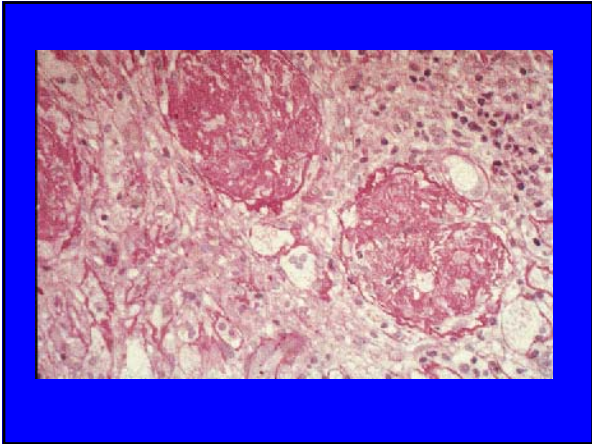
- Autoimmune disease involving multiple organ systems – joints, skin, kidney, brain, hematologic
- Organ inflammation is mediated by AUTOANTIBODIES and IMMUNE COMPLEXES

Pathogenesis of SLE: Overview

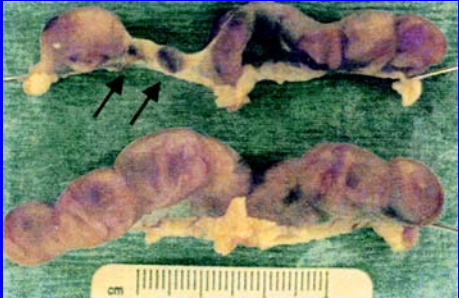


AUTOANTIBODIES PRECEDE DISEASE BY YEARS



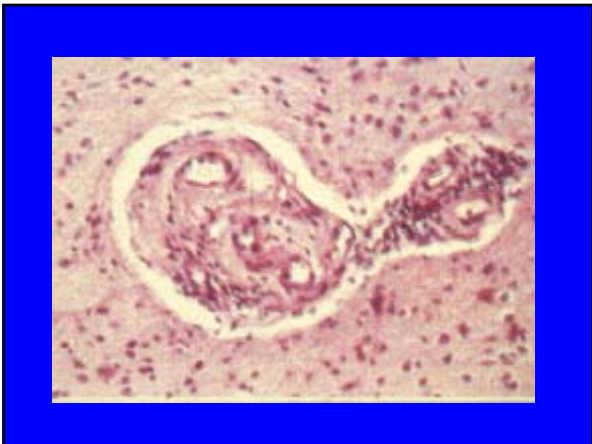


**Anti-PL induces Fetal Loss
Prevention with Crry-Ig**



Holers, Salmon et al, J Exp Med, 2002

The image shows two fetuses, one above the other, laid out on a green surface. A ruler is visible at the bottom for scale. Two black arrows point to specific areas on the fetuses, likely indicating sites of interest related to the study on anti-PL and fetal loss.



The Phases of SLE

- Genetic Predisposition
- Gender
- Environmental stimuli start Immune Responses (EBV)
- Autoantibodies Appear
- Regulation of the Autoantibodies Fails: Clinical disease
- Chronic inflammation, oxidative damage causes damage

CONCORDANCE FOR SLE IN TWINS

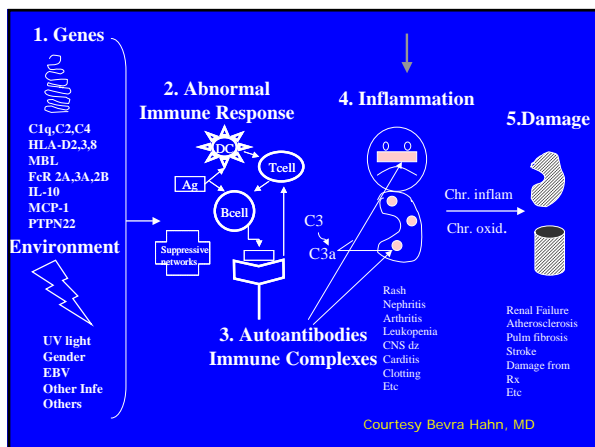
MONOZYGOTIC: 24-69 %

DIZYGOTIC: 2-9 %

Risk for Sibling of SLE: 10-20

Evidence that SLE is Influenced by Sex Hormones

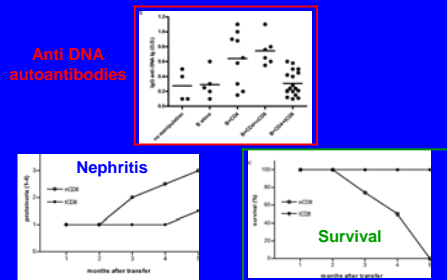
- 9:1 female:male ratio in child-bearing years
- Nurses' Health Study showed increased RR for SLE in women on HRT or OC.
- Treating women with SLE with HRT increases flares (OCP do not)
- Metabolism of E and A may be altered in women and men with SLE.
- Elevated levels of prolactin in some.
- Some mouse models influenced by E/A.



The Phases of SLE

- Genetic Predisposition
- Gender
- Environmental stimuli start Immune Responses (EBV)
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The Power of Regulation: Prevention of SLE by CD8 T_i induced by tolerogenic peptide



The Phases of SLE

- Genetic Predisposition
- Gender
- Environmental stimuli start Immune Responses (EBV)
- Autoantibodies Appear
- Regulation of the AutoAb Fails: Clinical disease
- Chronic inflammation, oxidative damage causes damage

ACR CRITERIA FOR SLE: 1997

- SKIN
 - malar rash
 - discoid rash
 - photosensitive rash
 - oral ulcers
- ARTHRITIS
- SEROSITIS
- NEPHRITIS
- NEUROLOGIC DIZ
- HEMATOLOGY DZ
 - leukopenia, lymphopenia
 - hemolytic anemia
 - thrombocytopenia
- IMMUNE DZ
 - anti-dsDNA
 - anti-Sm
 - any antiphospholipid
- ANA

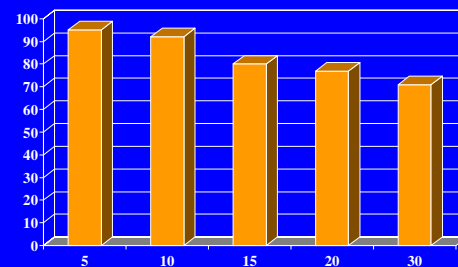
Any 4: Classify as SLE with 95% specificity; 80% sensitivity



TREATMENT GOALS

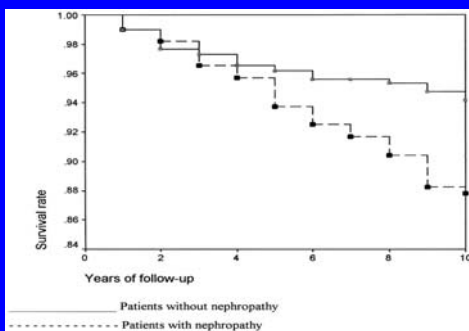
- Not Life Threatening
- Improve Pain, Fatigue, Rash
 - NSAIDs
 - Analgesics
 - Anti-Malarials (hydroxychloroquine – Plaquenil 200-400 mg qd
 - (Low dose prednisone)
- Life/Organ Threatening
- Survival with as Little Adverse Effects of Rx as possible
 - Prednisone high dose
 - Antimalarials
 - Cytotoxics: Mycophenolate (Cellcept), Azathioprine (Imuran), Cyclophosphamide (Cytosan)

Survival in SLE 2006



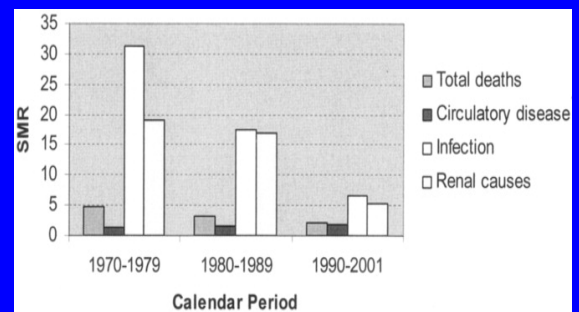
International; USA, Canada, Europe, Japan. Bernatsky S, 2006; Doria A, 2006; Funachi M, 2006; Chan TM, 2006; Kasitanon N, 2006; Cervera R, 2006.

Renal Involvement Increases Mortality



Cervera R, Medicine, 2003

Success: SLE Mortality is Declining

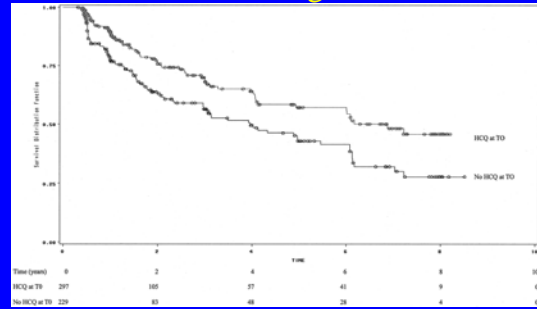


Bernatsky et al, Arthritis & Rheumatism, 2006.

“MILD” SLE

- 32 yo woman
- FATIGUE
- Photosensitive
- Arthritis occasionally
- WBC 3500
- ANA 1:80

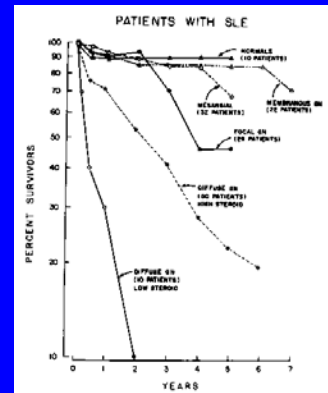
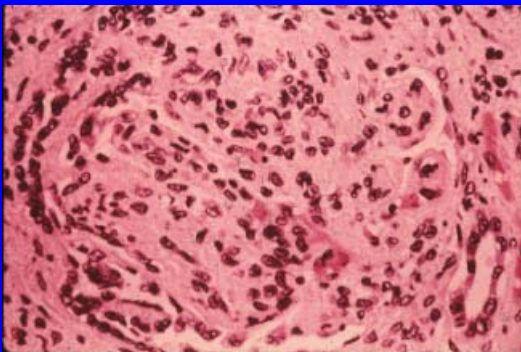
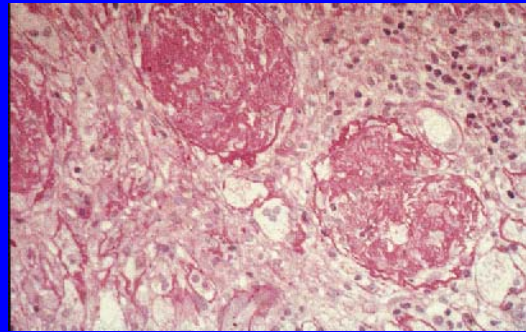
Hydroxychloroquine Reduces Damage



Fessler BJ et al, Arthritis Rheum, 2005

Life-Threatening SLE

- 25 year old woman, senior medical student
- SLE since age 16 with severe proliferative glomerulonephritis – treated with prednisone and cyclophosphamide (complic by miliary tuberculosis and fungal meningitis). Anti-DNA+, serum complement levels low
- Consult – renal failure. Lupus active or end stage?
- Immunosuppress or plan for transplant?



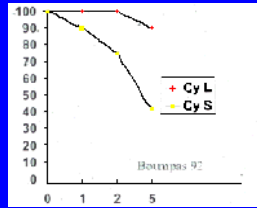
Cyclophosphamide in Severe GN

- Cyclophosphamide IV or PO Best to Preserve Renal Function

- 10 Yr Renal Failure

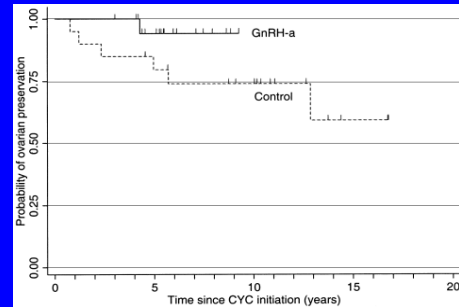
- Cy 10-20%
- Az 25%
- Pred 55%

• NIH Austin NEJM 86



Boumpas Lancet 1992

GNRH administration prior to IV Cytoxan Protects Ovaries: Lupron 3.75 mg sq 10-14 days before IV Cyt



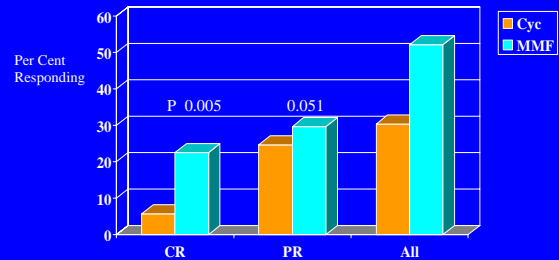
Open, not randomized, voluntary

Somers et al, A&R, 2005

Cyclophosphamide: Adverse Effects

- Infection (VZV): 37%
- Hair loss
- Nausea, diarrhea
- The Blues
- Gonadal failure
 - 6 months Rx: 20% of women >25 yo
 - 30 months Rx 65%

MMF is SUPERIOR to Cyc (6 mo) Induction of Response in Lupus GN



N 69C:71 MMF
5-1 g IV q mo C
1-3 g qd MMF

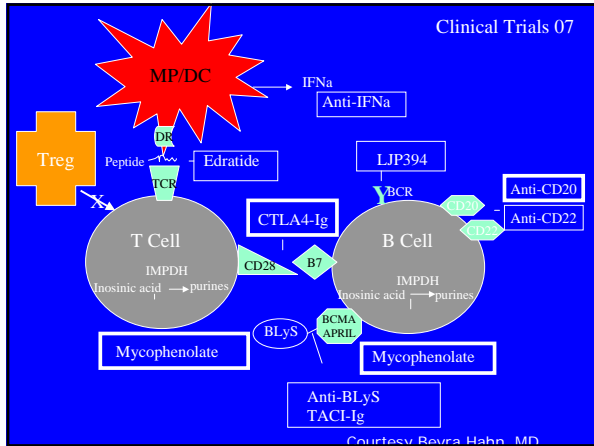
Ginzler E et al, N Eng J Med 05

Summary of Use of MMF > 6 mos

- Equivalent to or Better Than Maintenance of Improvement with Cyclophosphamide
- Less Toxic
- Azathioprine probably less effective in inducing and maintaining responses, but fewer serious adverse events.
- It is too early to abandon cyclophosphamide
- INFECTION WITH ALL: PREVENT INFE

Summary- Rx Lupus Nephritis 2007

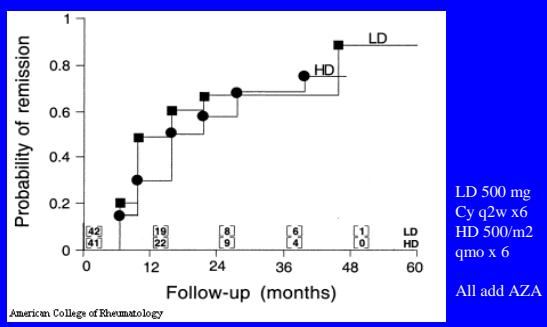
- **Induce** with Mycophenolate plus steroids: work up to 2-3 g/day MMF. Begin with pulse steroids then go to 0.5-1 mg/kg/d
- OR **Induce** with IV cyclophosphamide until clear response or for 6 months. Begin with pulse steroids, then go to 0.5-1 mg/kg/d. Lupron to protect ovaries
- **Maintain** with MMF (or azathioprine or Cyclophosphamide)
- Treat proteinuria/hypertension with ACE inhibitor or ACEi + ARB



EBV Associated with SLE?

- | | |
|-----------------------|--------------------|
| SEROCONVERSION | ODDS RATIOS |
| • Children | • Children |
| – 116/117 vs 107/153 | – 50 |
| • Adults | • Adults |
| – 195/196 vs 370/392 | – 9 |
- James et al, A & R 2001

Cyclophosphamide: Low and High Dose Give Similar Improvement

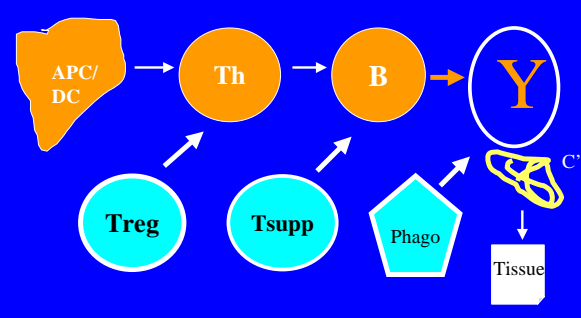


Houssiau et al, A&R 2002

The Phases of SLE

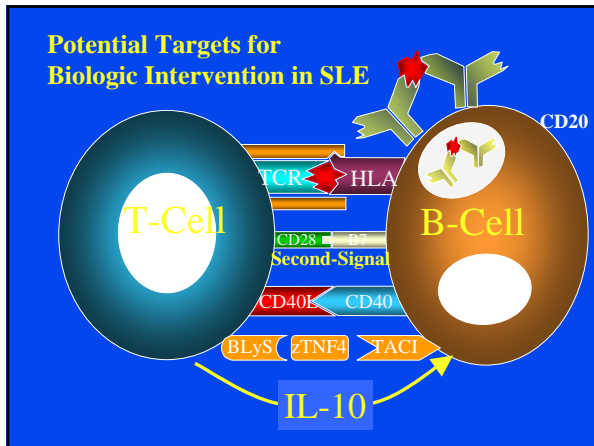
- Genetic Susceptibility
- Environmental Hits
- Abnormal Immune Response
- Autoantibodies
- Clinical Disease
 - Inflammation
 - Complement Activation
 - Cytokine/Chemokine Release
 - Proteolytic enzymes
- Chronic Damage
 - Chronic Inflammation
 - Chronic Oxidative Damage

TARGETS FOR REGULATION IN AUTOAb PRODUCTION



SLE - CAUSES OF DEATH

- | | |
|------------|--------|
| ACTIVE SLE | 15-50% |
| NEPHRITIS | 20-30% |
| INFECTION | 20-35% |
| STROKE, MI | 10-30% |



ImmunoREGULATION Deficits Allow SLE to Develop

- Treg
- CD8 Suppressor/Inhibitors
- NK T cell

Can be expanded in vitro

Crispin JC .03;Liu MF. 04; Wu HY. 04; Scalapino KJ.06, Filaci G.05; La Cava A . 04, Hahn BH.05; Horwitz D 01-06

AutoAb Precede SLE by YEARS

AUTOANTIBODIES PRECEDE DISEASE BY YEARS

Some AutoAb Before Dx: 88%

ANA: 3 yrs (9) Anti-Ro/La	anti-DNA: 2 yrs (9) anti-PL: (7)	anti-Sm: 1 yr (7) anti-RNP
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Arbuckle et al NEJM 2003