

# Newer Therapies for SLE and Dermatomyositis

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# Objectives

- Review current therapies for non-threatening and severe lupus
- Recent evidence based therapies for severe lupus
- Overview of future potential therapies for SLE
- Review current therapies for Dermatomyositis
- Discuss newer therapies for Dermatomyositis

# Disclosures

- I have no actual or potential conflict of interest in relation to this program/presentation.

# Therapies for SLE

- Mild Disease (non-life threatening): skin, joints, fatigue
  - Dihydroepiandrosterone
  - Antimalarials

# DHEA

- SLE patients have low plasma androgen
  - Contribution to immune dysregulation
  - Randomized trials: improvement of global assessment/disease flare
  - Recent DBRT: DHEA 100mg/200mg/placebo
    - 191 patients with SLE
    - No difference in endpoint of prednisone reduction
    - Subgroup: SLEDI >2 reduction in prednisone dose in group on 200mg
  - Side effects: acne, hirsutism, irregular menses, altered lipid profile

# Antimalarials and SLE

- Dermatological uses: hydroxychloroquine, chloroquine, quinacrine
- General management of SLE
  - Immunologic effects
  - Anti-thrombotic
  - Anti-platelet
  - Anti-inflammatory

# New Mechanism of Action of Antimalarials

- Role of toll-like receptors (TLR7,9) in SLE: pattern recognition receptors for DNA and RNA respectively
- Activation of these TLRs: increase IFN  $\alpha$ - from plasmacytoid dendritic cells and immunoglobulins from B cells
- Hydroxychloroquine: reduce activation of endosomal TLR by DNA or RNA

# Antimalarial and SLE

- Reduce risk of end-organ damage over time
- Reduce disease flares
- In patients with renal disease on immunosuppressives, better outcome in group with HCQ than control

# Toxicities of Hydroxychloroquine

- Retinal <3%
- Minimized by dosing <6.5mg/kg/day
- Neuropathy
- Myopathy
- Bone marrow effects

# Pregnancy and Hydroxychloroquine

- No RTC trials
- Retrospective data
- At doses used for rheumatic disease (200-400mg/d):
  - No increase in miscarriages or stillbirths
  - No congenital malformations
  - Prevents maternal flares

# Therapies for SLE

- Severe Disease
  - Traditional therapies
    - Glomerulonephritis
    - Non-renal disease
  - Newer therapies
    - Renal Disease
  - Biologic therapies
    - anti-B cell therapies
    - Anti-Tcell
    - Anti-cytokine
  - Stem cell transplantation

# Traditional Therapies

- Renal Disease
  - Treatment of proliferative glomerulonephritis best studied
    - Efficacy of IV cyclophosphamide established
    - Induction dosing regimen comparable between low dose (500mg/2 weeks for 3 months) vs. high dose (0.5-1gm/M<sup>2</sup> monthly for 6 month
    - Maintenance therapy with azathioprine after CYC
    - Similar efficacy at 73 months

# Traditional Therapies

- Non-renal disease
  - Few RCT
  - Based on renal disease studies
  - CNS disease: superiority of glucocorticoids and CYC;
  - Arthritis: MTX (one DBRCT), leflunomide, cyclosporin
  - Skin: calcineurin inhibitors; retinoids (SCLE); dapsone (bullous disease, panniculitis), thalidomide
  - IVIG: demyelinating syndromes; thrombocytopenias, peripheral neuropathies; other second line therapies

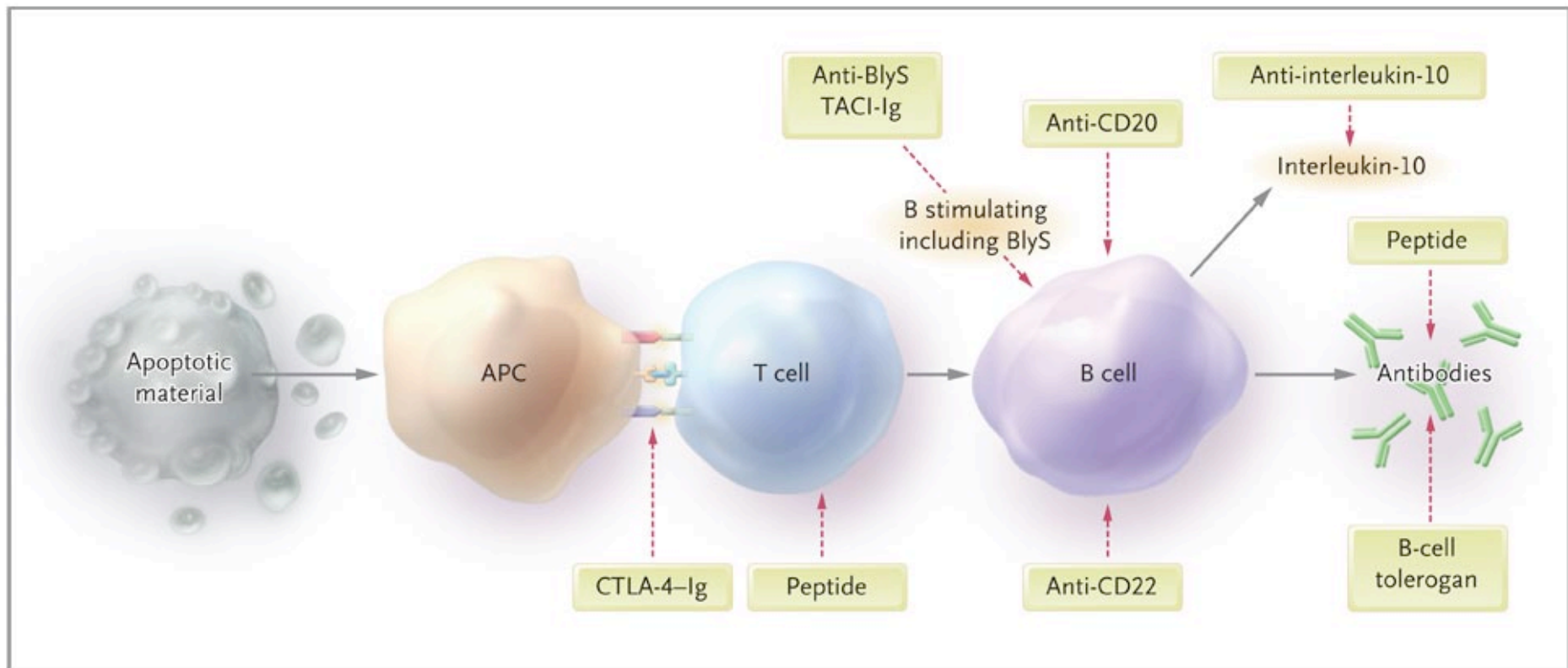
# Newer Therapy for SLE

- Renal disease
  - Mycophenolate mofetil (MMF)
    - Reversible inhibitor of inosine monophosphate dehydrogenase, enzyme involved in purine synthesis of activated T cell proliferation
    - Glomerulonephritis: Class III, IV, V
    - Ginzler et al 2006 (open-label, RC): MMF more effective and safer than traditional IV CYC inducing remission with =in 24 weeks
    - Recent open-label RC international study (ALMs): no difference in efficacy or safety (but non-Caucasian/Asians responded more to MMF)
    - Efficacy in maintaining remission comparing to AZA pending

# Cautions regarding MMF

- Toxicities
  - Gastrointestinal (nausea, diarrhea)
  - Bone marrow suppression (neutropenia)
  - Late development of malignancy
  - Recent reports progressive multi-focal leukoencephalopathy due to reactivation of the polyomavirus JC (JCV)
- Contraindication
  - Pregnancy: teratogenic
- No long term data (>5 years)

# Targeted Therapeutic Approaches in Systemic Lupus Erythematosus



Rahman A and Isenberg D. N Engl J Med 2008;358:929-939



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# B-cell Depletion Therapies

- Rituximab (anti-CD 20)
  - CD20: B cell surface marker for maturing B cells except for plasma and early precursor cells
  - Chimeric monoclonal antibody against CD20
    - Mouse variable portion
    - Human IgG1 and k light chain constant region
  - Mechanism of action:
    - Induce apoptosis
    - Complement mediated cytotoxicity
    - Fc receptor mediated cell-mediated cytotoxicity

# B-cell Depletion Therapies

- Rituximab in SLE
- Open label, uncontrolled studies/case series
  - Favorable outcomes in range of refractory disease: nephritis, CNS disease, vasculitis, thrombocytopenia
  - Study of combination of rituximab and CYC in 32 refractory patients: 1/3 sustained clinical remission for 3 years in followup

# B-cell Depletion Therapies

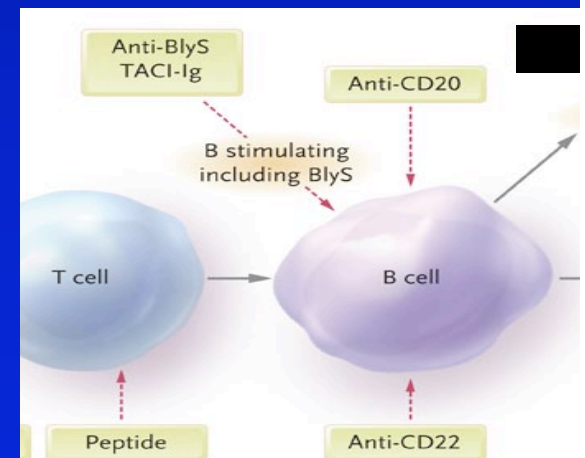
- Length and depth of depletion correlates to biological response
- Baseline B cell phenotype in patients may predict response
- No alteration of immunoglobulin production or protective antibodies
  - No or variable changes in anti-DNA or ANA titers
- Mechanism of action: alteration in B cell function in co-stimulation of T cells or cytokine production

# B-cell Depletion Therapies

- Need for large scale RCT studies: currently underway
- Concerns about rituximab:
  - Reports on 2 deaths related to progressive multi-focal leukoencephalopathy (PML) in SLE patients (also exposed to CYC)
  - Length or frequency of retreatment?
  - Long term risk for infections?
  - Risks in combination therapy

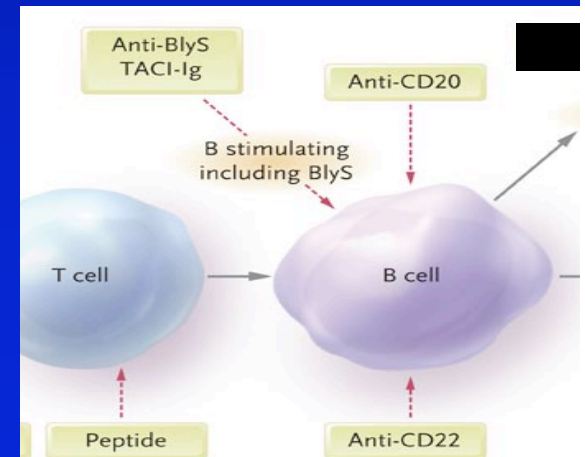
# B-cell Depletion Therapies

- Epratuzumab
  - Humanized monoclonal Ab against CD22
  - CD22 also B-cell surface marker
  - Temporary reduction in B-cells
  - Phase II studies small, open label: modest improvement
  - Phase III trials to start



# B-cell Depletion Therapies

- B-lymphocyte stimulator protein (BlyS) or (BAFF)
  - Soluble protein within family of tumor necrosis factor
  - Binds to surface receptors of activated B cells
    - B-cell proliferation and survival
    - B-cell differentiation into plasma cells
  - Higher levels (seen in active SLE patients) may contribute to autoantibody generation
    - B-cell proliferation and survival
    - B-cell differentiation into plasma cells



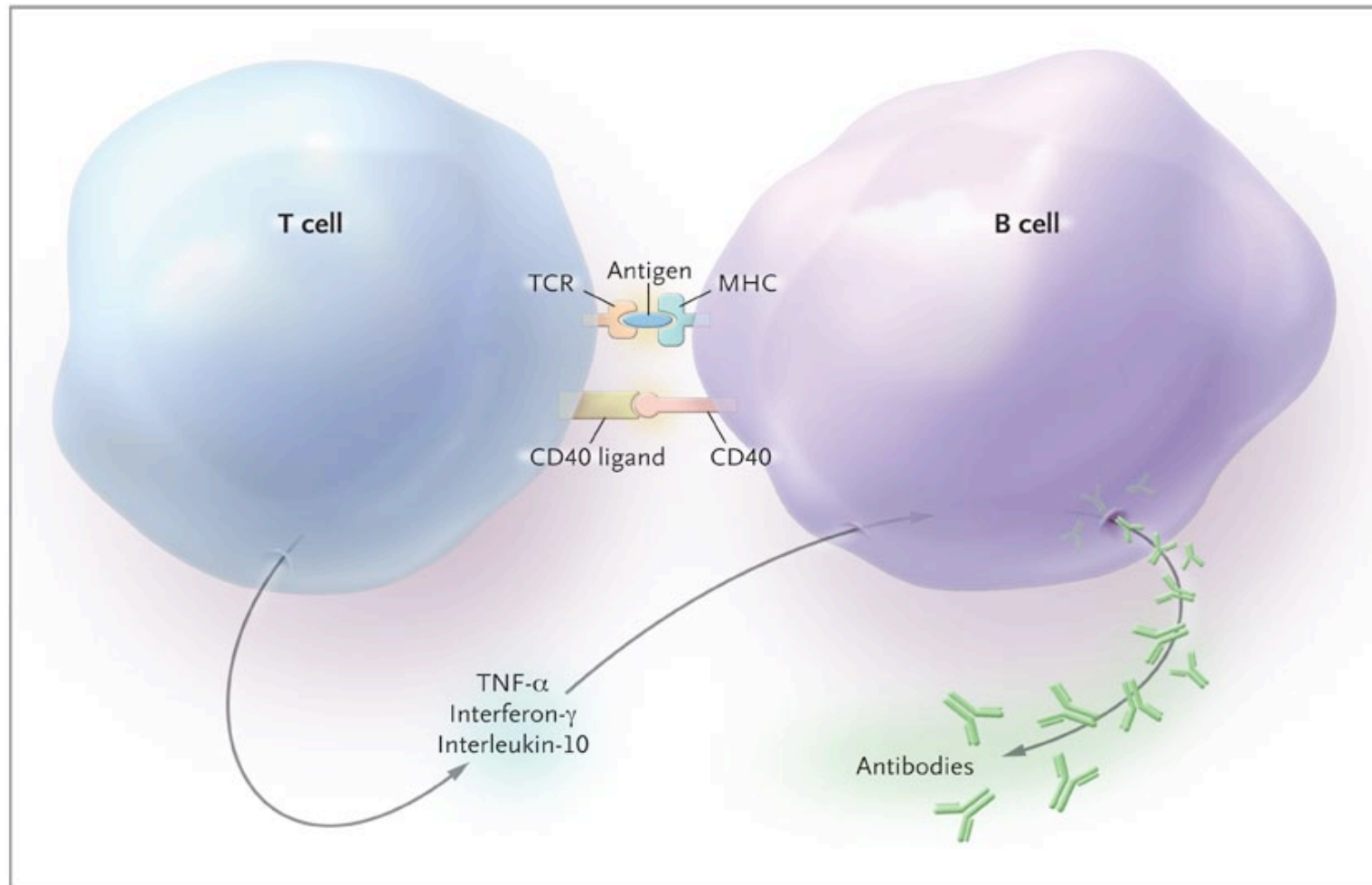
# B-cell Depletion Therapies

- Belimumab: human monoclonal Ab against BlyS
  - Phase II RCT: drug & standard of care vs. placebo & standard of care—patients with measurable DNA or ANA levels responded by standardized scores, lower anti-DNA, and reduction in immunoglobulins
  - Phase III trials under way
- Atacicept: soluble receptor fusion protein of TACI-IgG that reduce soluble BlyS

# Unanswered questions in B cell depletion

- ? Resetting of B cell repertoire after B cell depletion
- Clones that resist depletion: ? dominate in peripheral circulation

# T Cell-B Cell Interaction



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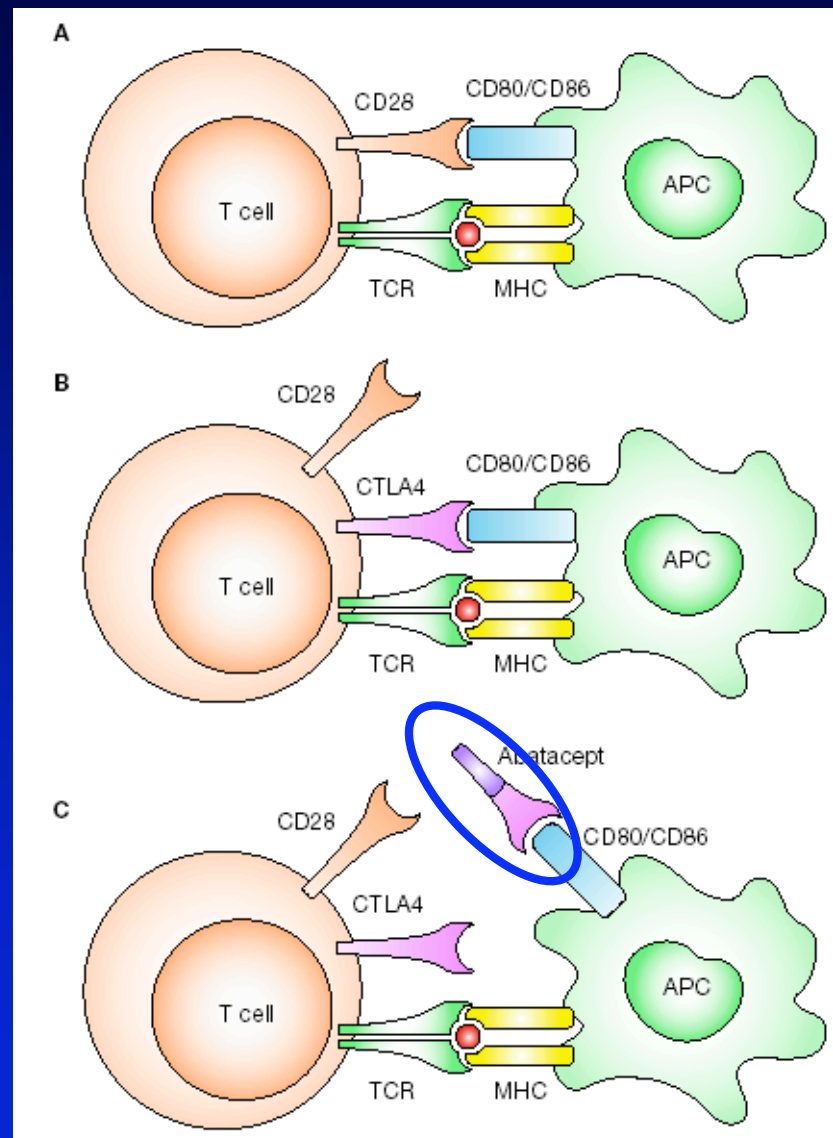
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# T cell Targets

- Induction of anergy (non-responsiveness) in T or B cells may reduce immune response in SLE disease state
  - Abatacept: receptor fusion protein that blocks interaction of antigen presenting cells (APCs) with T cell; inhibition of this co-stimulation prevents activation of T cells, subsequent cytokine production, and B cell activation
  - Trials currently underway

T-cell activation requires interaction between the T-cell receptor and antigen in the context of MHC molecules on the APC plus a second co-stimulatory signal

Abatacept interrupts the interaction between CD80/CD86 and CD28 or CTLA4, thereby disrupting the second signal to the T cell.



Expression of CTLA4 is upregulated on the T cell following activation.

Binding of CTLA4 to CD80/CD86 provides a control signal that suppresses ongoing T-cell activation.

# Therapies Inducing Tolerance

- SLE characterized by loss of tolerance against self-antigens
- “Tolergens” use anergic principles
  - LJP 394 (abetimus sodium) synthetic tolerogen against anti-DNA B cells
    - Cross links surface receptors of B-cell that make anti-DNA
    - Binding is first signal but no second signal: B cell is inactivated and no subsequent Ab production

# Abetimus Sodium (LP 394)

- Recent trial DB, RCT vs. placebo
- Weekly 100 mg resulted in significant and persistent reductions in anti-DNA titers
- End point not met since no prolongation in time to renal flare but 25% fewer renal flares occurred in the abetimus group compared with the placebo; decrease in proteinuria
- Safety profile

# Anti-Cytokine Therapies

- Given the role of IFN- $\alpha$  in SLE, antibodies are possible therapeutic strategies
  - Phase II trials currently with MEDI-545
- Anti-IL-6: along with INF  $\alpha$  stimulate maturation of plasma cells
  - Tocilizumab recently approved for RA
  - Trials in use of SLE

# Anti-TNF Therapies in SLE

- Infliximab
  - Open Label Studies
  - Efficacy in arthritis, skin, nephritis
  - Nephritis: effective in 4 infusions
  - Short-term: antibodies against DNA
  - Phase III trial currently in progressive for lupus nephritis

# Autologous Hematopoietic Stem Cell Transplant

- Therapy for refractory SLE
  - High dose chemotherapy to ablate auto-reactive B and T cells
  - Shorten duration of cytopenias
  - Transplanted progenitors recognize self Ag in bone marrow and thymus and develop tolerance

# Autologous Hematopoietic Stem Cell Transplant

- Indications
  - Refractory nephritis, cerebritis/myelitis, lung disease, or hematologic disease
- Outcomes of 100 patient world-wide
  - 66-92% initial remission
  - 50% 5-year disease-free survival
  - One center: 2% treatment mortality; 16% overall mortality at 5 years





# Treatment of Dermatomyositis

- Traditional Therapies
  - High dose steroids (0.5mg-1.5mg/kg/d)
    - No RCT but case reports and series
    - Daily vs. alternate day dosing vs IV pulse
    - Maintain for 1 mo., taper after 2-4 wks by 10mg/mo
    - Toxicities

# Treatment of Dermatomyositis

- Combination therapy (Randomized trials but small numbers)
  - Steroids with azathioprine at 2.5mg/kg (57-77%)
  - Steroids with methotrexate 15-25mg/wk (70-77%)
  - Combination of oral MTX and AZA
  - Used as steroid sparing effects as well
  - MTX may have better side effect profile

# Cyclosporine A in Dermatomyositis

- Use if contraindications or failure with MTX or AZA
- Role in interstitial lung disease?
- Limited studies (randomized trials)
  - RCT: CyA vs. MTX in background of steroids
  - Improvement in both groups
  - 6 mo follow-up: no difference in effects

# Treatment of Dermatomyositis

- Intravenous Immunoglobulin (IVIg)
  - Mechanism
    - Unknown
    - Dose: 2gm/kg
  - Evidence based medicine
    - Treatment resistant DM: placebo controlled: high doses better than placebo
    - Short term effects (6 weeks)
    - Costly

# Treatment of Dermatomyositis

- Cyclophosphamide
  - Variable results
  - Anecdotal evidence
  - Subset of patients with interstitial lung disease
    - 40% may benefit (IV monthly)
    - Utility in in rapid onset of lung disease
- No role for plasma exchange

# Treatment of Dermatomyositis

- Mycophenolate mofetil
  - Effects possibly related to inhibition of B and T lymphocyte proliferation
  - Small case series: effective for cutaneous and muscle disease
  - Infectious complications

# Treatment of Dermatomyositis

- Biologics
  - Rituximab (Case reports)
    - B cell blockade
    - Treatment resistant or early onset
    - Not clear benefit on skin
  - Anti-TNF $\alpha$ 
    - Inconsistent results (Clinical series)
    - Worsening in some patients

# Additional Considerations

- Physical therapy
  - Guided rehabilitation/therapy once muscle disease under control with immunotherapy
  - Optimal design of exercise remains to be determined
- Skin Disease (mostly clinical series)
  - Hydroxychloroquine
  - Topical tacrolimus

# Summary

- New insights on mechanism of traditional therapies in SLE
- Evidence based support of MMF in SLE
- New biologics in the horizon in treatment of SLE
- Limited new therapies in Dermatomyositis