Best Practices: Initial Treatment of SLE and GCA

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Classification Systemic Lupus Erythematosus: ACR 1997

- 1. Malar Rash
- 2. Discoid rash
- 3. Photosensitivity
- 4. Oral ulcers
- 5. Nonerosive Arthritis (> 2 peripheral)
- 6. Pleurisy/Pericarditis
- 7. Renal: persistent proteinuria >0.5g/d or >3+ dipstick or cellular casts.
- 8. Neurologic Disorder: seizures or psychosis in absence of other causes
- 9. Hematologic Disorder: hemolytic anemia, Leukopenia <4,000/mm3, Lymphopenia <1500/mm3, Thrombocytopenia <100,000/m3
- Immunologic: dsDNA, Anti-Smith, or ACA IgG or IgM, +LA, false + RPR with confirmation FTA.
- + ANA

Classification Systemic Lupus Erythematosus: SLICC 2012

- **Biopsy + Lupus Nephritis and +ANA or +dsDNA sole criterion for SLE**
- **Immunological Criteria**
  - 1. ANA +
  - 2. dsDNA (ELISA 2x ULN)
  - 3. Anti-Smith
  - 4. Antiphospholipid Ab: LA, false + RPR, ACA any subtype in moderate to high titer, B2-Glycoprotein any subtype
  - 5. Low C3, C4 or CH50
  - 6. Direct Coombs test + in absence of Hemolytic anemia

At least 4 : one Immunologic and one Clinical

- **Clinical Criteria**
  - Acute Cutaneous Lupus:
  - Chornic Cutaneous lupus:
  - Oral/Nasal Ulcers
  - Nonscarring Alopecia
  - Synovitis of >2 joints or Morning stiffness
  - Serositis
  - Renal: U/Pr spot or 24 hr >500mg or RBC casts
  - Neurologic: seizures, psychosis, Mononeuritis multiplex, myelitis, neuropathy, confusional state
  - Hemolytic anemia
  - Leukopenia <4,000/mm3 OR Lymphopenia <1,000/mm3
  - Thrombocytopenia <100,000/mm3

Petri, M; Orbai, A; et al *Arthritis Rheum* 2012 August: 64 (8) 2677-2686

Quick Mneumonic

- **ACR 1997**
- **S**erositis
- **O**ral ulcers
- **A**rthritis
- **P**hotosensitivity
- **B**lood disorders-anemia, leukopenia, lymphopenia
- **R**enal
- **A**NA
- **I**mmunologic: Smith or dsDNA, ACA, RPR false +
- **N**eurological
- **M**alar rash
- **D**iscoid rash

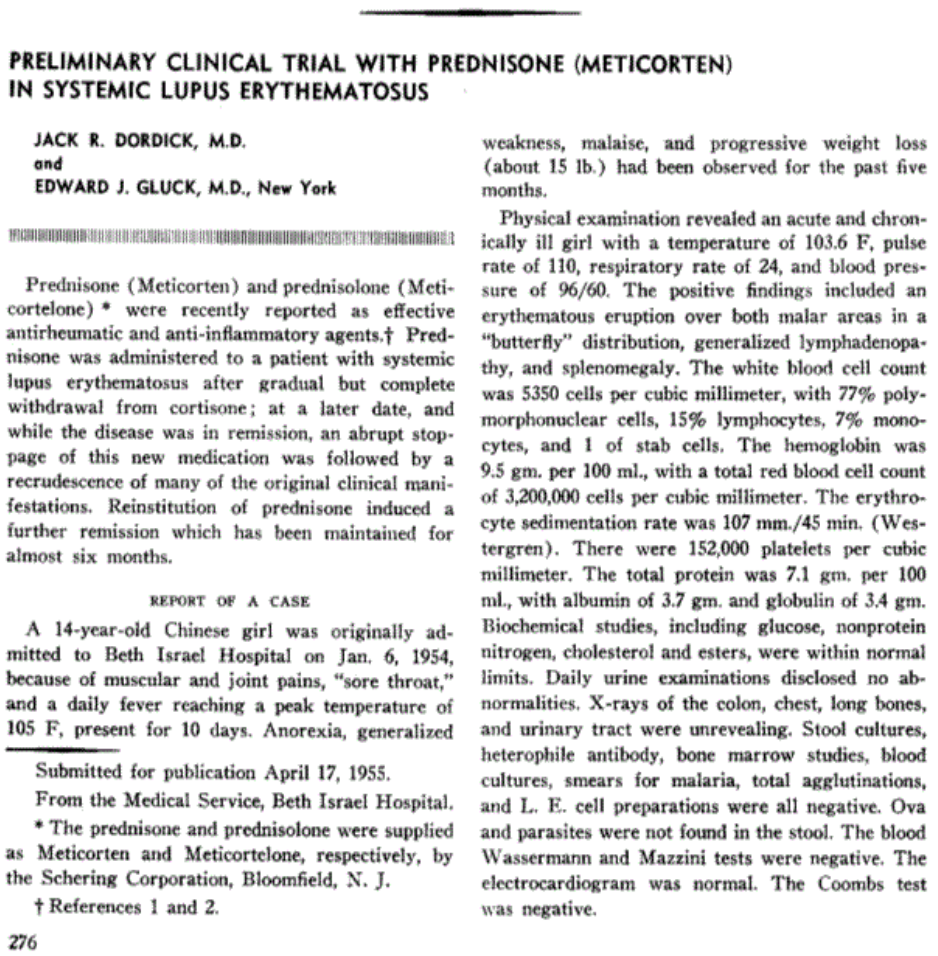
- **SLICC 2012**
- **R**enal
- **A**lopecia
- **S**erositis
- **H**emolytic anemia
- **O**ral and nasal ulcers
- **N**eurologic
- **S**ynovitis
- **C**hronic Cutaneous Lupus
- **A**cute Cutaneous Lupus
- **L**eukopenia/Lymphopenia
- **P**latelets, low

Treatment Principles:

- Goals:
  - Control ongoing inflammation
  - Restrict irreversible end-organ damage
  - Maintain QoL
- Choosing Therapy based of severity of disease and specific organ involved
- Treat to Target in SLE 2014: There is never just one target in SLE.

FDA indicated medications

- 1948: Aspirin approved by the FDA to treat SLE
- 1955: Prednisone was approved for use of
- 1955: Hydroxychloroquine
- 2011: Benlysta



PRELIMINARY CLINICAL TRIAL WITH PREDNISONE (METICORTEN) IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Prednisone (Meticorten) and prednisolone (Meticortelone) * were recently reported as effective antirheumatic and anti-inflammatory agents.† Prednisone was administered to a patient with systemic lupus erythematosus after gradual but complete withdrawal from cortisone; at a later date, and while the disease was in remission, an abrupt stoppage of this new medication was followed by a recrudescence of many of the original clinical manifestations. Reinstitution of prednisone induced a further remission which has been maintained for almost six months.

REPORT OF A CASE

A 14-year-old Chinese girl was originally admitted to Beth Israel Hospital on Jan. 6, 1954, because of muscular and joint pains, "sore throat," and a daily fever reaching a peak temperature of 105 F, present for 10 days. Anorexia, generalized weakness, malaise, and progressive weight loss (about 15 lb.) had been observed for the past five months.

Physical examination revealed an acute and chronically ill girl with a temperature of 103.6 F, pulse rate of 110, respiratory rate of 24, and blood pressure of 96/60. The positive findings included an erythematous eruption over both malar areas in a "butterfly" distribution, generalized lymphadenopathy, and splenomegaly. The white blood cell count was 5350 cells per cubic millimeter, with 77% polymorphonuclear cells, 15% lymphocytes, 7% monocytes, and 1 of stab cells. The hemoglobin was 9.5 gm. per 100 ml., with a total red blood cell count of 3,200,000 cells per cubic millimeter. The erythrocyte sedimentation rate was 107 mm./45 min. (Westergren). There were 152,000 platelets per cubic millimeter. The total protein was 7.1 gm. per 100 ml., with albumin of 3.7 gm. and globulin of 3.4 gm. Biochemical studies, including glucose, nonprotein nitrogen, cholesterol and esters, were within normal limits. Daily urine examinations disclosed no abnormalities. X-rays of the colon, chest, long bones, and urinary tract were unrevealing. Stool cultures, heterophile antibody, bone marrow studies, blood cultures, smears for malaria, total agglutinations, and L. E. cell preparations were all negative. Ova and parasites were not found in the stool. The blood Wassermann and Mazzini tests were negative. The electrocardiogram was normal. The Coombs test was negative.

Submitted for publication April 17, 1955.
From the Medical Service, Beth Israel Hospital.

* The prednisone and prednisolone were supplied as Meticorten and Meticortelone, respectively, by the Schering Corporation, Bloomfield, N. J.

† References 1 and 2.

Do we have a single treatment algorithm?

- Treatment has been typically organ/symptoms focused.
- ACR 1999 Guideline
- 2010 EULAR Rec on Management of Neuropsychiatric Lupus
- ACR 2012 Lupus Nephritis
- EULAR 2012 Lupus Nephritis
- Treat to Target in SLE 2014
  - How to we treat an ever changing target?
  - How do we define remission?

Treat to Target Recommendations

- 1. SLE target: remission or lowest achievable disease activity
- 2. Prevention of flares
- 3. Not rec asymptomatic patients need treatment escalation
  - Ok to have persistence of serologies
- 4. Prevention of damage
- 5. Fatigue, pain and depression should be addressed/QoL
- 6. Early diagnosis of renal disease: check UA and pro/cr every 3-4 months
- 7. Lupus nephritis: treatment for 3 years once maintanence achieved
- 8. Lupus maintenance at lowest effective dose of GC
- 9. APS must be addressed and treated (16% of SLE patients)
- **Irrespective of other treatment antimalarial on all patients**
- **Relevant therapies adjunctive to immunomodulation should be considered***

Standard Medications

- NSAIDs +
- Corticosteroids +
- Antimalarials +
- Azathioprine
- Methotrexate *
- Mycophenolate mofetil
- Dapsone
- Topical therapy
- Cyclosporine
- Cyclophoshamide
- Leflunomide *
- Thalidomide *
- IVIG
- Benlysta +
- * Case Reports/Small or conflicting studies
- + Have FDA indications

Cornerstone: Hydroxychloroquine

- Commonly 1st line in mild SLE; arthritis, skin
- Even if on other immunosuppressant if they tolerate HCQ they continue HCQ
- May take up to 6 weeks for response & 4 mos for peak efficacy
- Prevention of flares
- Low serum levels of HCQ in nonadherence is predictive of disease flares in SLE patients
- Postive effect on lipid profiles in SLE patients
- May play roll in reducing CV and thrombotic risk
- Retinopathy- baseline visual field exam and annual (AAOS)

Hydroxychloroquine

- Down regulation of Toll like receptor -The result is decreased inflammatory cytokine production and antigen processing necessary for antigen presentation of autoantigens.
- Cigarette smoking may interfere with response to antimalarial in discoid LE and subacute LE
- AE: GI SE-transient, retinal toxicity (blurred vision, photophobia)
  - blue-gray to dark purple skin discoloration on sun-exposed skin
  - Hemolytic anemia if G6PD deficiency

NSAIDs

- Indications: arthritis, myalgia, serositis, and headache
- Inhibits inflammatory reactions and pain by decreasing prostaglandin synthesis
- Many options choose based on your patient
- Monitor for renal, hepatic or CNS toxicities
  - -CNS?!, yes aseptic meningitis can be caused by NSAIDS

Corticosteroids

- Decreases inflammation by reversing increased capillary permeability and suppressing PMN activity. Stabilizes lysosomal membranes and suppresses lymphocytes and antibody production
- Mild to moderate SLE:
  - Cutaneous disease, arthritis, and serositis.
  - 5-30 mg equivalent dose of prednisone in single or divided doses daily
- Severe organ involvement
  - Nephritis, pneumonitis, hematologic abnormalities, CNS disease, & systemic vasculitis
  - high dose in PO or IV equivalent of prednisone of 1 to 2 mg/kg/day
  - Pulse: Methylprednisolone 1g IV daily x 3 days

When to pulse in SLE

- **General rule of thumb: Life Threatening Events**
  - **The general rationale is to induce remission quickly with lasting effect and eliminate protracted course of Prednisone with adverse side effects**
- Transeverse Myelitis/CNS Lupus
- Vasculitis
- Diffuse alveolar Hemorrhage/Severe lupus pneumonitis
- Refractory ITP
- Lupus Nephritis (some cases)
- Catastrophic APS

Azathioprine

- Antagonizes purine metabolism and inhibits nucleic acid synthesis affecting both cellular and humoral function
  - Used in mild to moderate SLE and as alternative maintenance tx to cyclophosphamide in lupus nephritis or other organ-threatening involvement
  - Milder cases of Lupus Pneumonitis, Lupoid Hepatits, Myocarditis, SCLE some studies.
  - No evidence found to show that AZA is useful in management of acute, severe exacerbations, but AZA treated groups show decreased mortality and morbidity with this steroid sparing agent.
- 1 mg/kg/d PO divided BID for 6-8 wk, increase by 0.5 mg/kg q4wk until response up to max dose 2.5 mg/kg/d
  - Can take 6-8 weeks for full effect
  - Maintenance: decrease 0.5 mg/kg/day q4-8wk as able
- Can be used during pregnancy

Azathioprine

- AE: GI toxicity, acute myelotoxicity (TPMT deficiency), pancreatitis
  - Allopurinol inhibits XO and induces toxicity and acute pancytopenia.
    - Adjust dose of AZA as **allopurinol** potentiates (cut dose in half).

- Lab
  - Baseline: CBC, plt, Cr, AST, ALT, Hepatitis B & C serology
  - CBC, plt every 1-2 weeks w/ dose change then monthly; Cr, AST, ALT every 1-3 mos afterwards

Methotrexate

- Dihydrofolic acid analog which inhibits dehydrofolate reductase and has immunomodulatory effects.
  - Numerous case studies and retrospective studies have demonstrated success in the treatment of active cutaneous and articular manifestations allowing steroid sparing.
  - Conflicting results as to benefit in SLE
- 7.5-25 mg PO/IM weekly
- AE: GI complaints, mucositis, alopecia, LAE elevations, and myelosuppression, infection
  - Hepatotoxicity esp. with EtOH
  - Pneumonitis, rare but life-threatening, pulm fibrosis
  - Teratogenic-D/C 6 mos prior to pregnancy in M and F
- CBC and CMP every 8 weeks x3 then every 12 weeks therafter.

Cyclophosphamide

- Alkylating agent -the MOA of the active metabolites may involve cross-linking of DNA, which may interfere with growth of normal and neoplastic cells
- Severe SLE with end-organ damage
- Nephritis, cerebritis, pulmonary hemorrhage, vasculitis
- 500-750 mg/m2 IV qmo

Cyclophosphamide

- AE: N/V, alopecia, bone marrow suppression, infection, hemorrhagic cystitis, bladder CA, lymphoproliferative d/o
  - risk for cervical dysplasia and CIN
  - Infertility- advanced age, cumulative dose
  - Mesna
  - Allopurinol may increase risk of bleeding or infection and enhance myelosuppressive effects
- Lab
  - Baseline: CBC, Cr, AST, ALT, Hep B & C serology, UA
  - Monthly: CBC, plt, AST, ALT, Cr, UA (if hematuria urology eval); yearly cytology

Mycophenolate Mofetil (CellCept)

Inactive prodrug of MPA, inhibits inosine monophosphate dehydrogenase (IMPDH), lymphocyte proliferation, and both T- and B-cell function

→Effective for lupus nephritis and

←**As effective as cyclophosphamide in inducing short-term remission with better safety profile**

→**Titrate to 1 g PO BID (500mg to 1500mg BID)**

ACR Guidelines Treatment of Lupus Nephritis 2012

IVIG

→Neutralizes circulating myelin antibodies through anti-idiotypic antibodies. Blocks Fc receptors on macrophages, inhibits complement, suppresses inducer T and B cells, and augments suppressor T cells

→Serious SLE flares

→**2 g/kg IV over 2-5 d**

Rituxan

Rituximab-chimeric momoclonal Ab that binds CD20 on the surface of B cells causing B-cell depletion

- Efficacy and Safety of Rituximab in Patients with Severe SLE (EXPLORER)
- LUNAR (The Efficacy and Safety of Rituximab in class III or IV lupus nephritis)
- Multiple open-label studies report the efficacy of RTX in patients w/ severe refractory SLE and CAPS

→Epratuzumab-human mab that targets CD22 on B cells causing modulation but not depletion

Belimumab

- B-cell activating factor (BAFF)/B-cell stimulator (BlyS) modulate B-cell survival and maturation
  - Member of TNF superfamily
- Most improved in pts with high anti-dsDNA and low C3
- Two large randomized, double-blind, placebo-controlled, multicenter phase 3 trials, BLISS-52 and BLISS-76
  - 865 and 826 seropositive (ANA &/or anti-dsDNA)
  - Randomized to receive 10 mg/kg belimumab, 1 mg/kg belimumab, or placebo
- Belimumab achieved significantly better results than placebo in both studies
  - significantly delayed time to first SLE disease flare versus placebo and lead to significant reduction in steroid doses in BLISS-52
  - well tolerated, with rates of overall adverse events, serious adverse events, infections and fatalities comparable between belimumab and placebo groups

Organ Involvement	First Line or Induction	2nd Line Induction failure	Third-line	Maint.	Ancillary	%Agreement
Constitutional Symptoms	GC, HCQ, IMM or combinations	MMF	RTX or BLM	N/A	N/A	60
Non-erosive , non deforming polyarthritis	HCQ ± HCQ	MTX	RTX		NSAIDs	80
Lupus pericarditis	GC +/- HCQ	MMF, AZA, MTX	RTX or BLM		Pericardiocentesis	75
Discoid Lupus erythematosus	HCQ +/- GC	Add AZA	MMF or MTX		Sunscreen + topical steroids	70
Lupus ILD	GC + MMF or IV CYC	RTX or IVIG	N/A	AZA or MMF		80
Thrombocytopenia	GC +/- HCQ	Add AZA or MMF	Add RTX, or IV CYC or IVIG		Splenectomy	50
Uncomplicated digital/cutaneous vasculitits	GC +/- HCQ +/- MTX	AZA or MMF	IV CYC			80

Muangchan, C. , van Vollenhoven, et al *Treatment Algorithms in Systemic Lupus Erythematosus*. Arthritis Care & Reaseasrch, Vol 67 (9) September 2015, p 1237-1245

Best Practices for Giant Cell Arteritis

Giant Cell Arteritis

- Most common primary systemic vascultitis in adults >50
- Large vessel vasculopathy.
- Persistent inflammation can cause stenosis or aneurysm
- Visual loss 10%
- Relapse in 50% when taper begins
- North America: 15-20% of PMR have coexistent GCA.
- 40-60% of GCA have coexistent PMR.

Giant Cell Arteritis

- **1990 CRITERIA FOR THE CLASSIFICATION OF GIANT CELL (TEMPORAL) ARTERITIS - EXCERPT**
  - 1. Age at disease onset >=50 years
  - 2. New headache
  - 3. Temporal artery abnormality
  - 4. Elevated erythrocyte sedimentation rate
    - Erythrocyte sedimentation rate >=50 mm/hour by the Westergren method
  - 5. Abnormal artery biopsy
    - Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells
  - * For purposes of classification, a patient shall be said to have giant cell (temporal) arteritis if at least 3 of these 5 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%

Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122---8.

Prednisone

- The gold standard for therapy
- 1mg/kg of body weight per day (typically 60mg)
- For high risk of potential vision loss- IV pulse therapy Solumedrol 1,000mg x 3 days
- Once CRP reduced by 50% can wean Prednisone by 10-20% every 2 weeks to 10mg daily, then reduction by 1mg/month
- BSR GuidelinesSuggested tapering regimen:
  - 40–60mg prednisolone continued until symptoms and laboratory abnormalities resolve (at least 3–4 weeks)
  - then dose is reduced by 10mg every 2 weeks to 20 mg;
  - then by 2.5mg every 2–4 weeks to 10 mg; and
  - then by 1mg every 1–2 months provided there is no relapse.

Aspirin

- Consideration of 81mg -150mg suggested as possible reduction in risk of ischemic complications of GCA *
  - * No RCT to support this. Observational only

Methotrexate

- recommended in GCA with multiple relapses.
- Reduced relapse rates by 35%
- meta-analysis of the methotrexate studies44 reanalyzed the pooled data and revealed a benefit for oral methotrexate 7.5 to 15 mg/week over placebo in preventing both first and second relapses of GCA and in reducing the cumulative corticosteroid dose by 48 weeks.

The search for steroid sparing therapy

- Remicade : studies did not show significant benefit
- Rituximab: Case reports.

The role of IL-6 inhibition

- As of May 2017 Actemra (tocilizumab) received FDA indication in the treatment of GCA
- Kevzara is a newer IL-6 inhibitor with likely trial for GCA in the future.

Questions?