Best Practices: Initial Treatment of SLE and GCA

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RHEUMATOLOGY
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

- **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

At least 4: one Immunologic and one Clinical

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

- ACR 1997
  - Serositis
  - Oral ulcers
  - Arthritis
  - Photosensitivity
  - Blood disorders-anemia, leukopenia, lymphopenia
  - Renal
  - ANA
  - Immunologic: Smith or dsDNA, ACA, RPR false +
  - Neurological
  - Malar rash
  - Discoid rash

- SLICC 2012
  - Renal
  - Alopecia
  - Serositis
  - Hemolytic anemia
  - Oral and nasal ulcers
  - Neurologic
  - Synovitis
  - Chronic Cutaneous Lupus
  - Acute Cutaneous Lupus
  - Leukopenia/Lymphopenia
  - Platelets, low
Treatment Principles:

- Goals:
  - Control ongoing inflammation
  - Restrict irreversible end-organi damage
  - Maintain QoL

- Choosing Therapy based on severity of disease and specific organ involved
- Treat to Target in SLE 2014: There is never just one target in SLE.
1948: Aspirin approved by the FDA to treat SLE
1955: Prednisone was approved for use of
1955: Hydroxychloroquine
2011: Benlysta
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?
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 maintenance 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
- Cyclophosphamide
- Leflunomide *
- Thalidomide *
- IVIG
- Benlysta +
- * Case Reports/Small or conflicting studies
- + Have FDA indications
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

Positive effect on lipid profiles in SLE patients

May play role 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 Hepatitis, 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 thereafter.
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)
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
Rituximab-chimeric monoclonal 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
<table>
<thead>
<tr>
<th>Organ Involvement</th>
<th>First Line or Induction</th>
<th>2\textsuperscript{nd} Line Induction failure</th>
<th>Third-line</th>
<th>Maint.</th>
<th>Ancillary</th>
<th>%Agreement</th>
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<tbody>
<tr>
<td>Constitutional Symptoms</td>
<td>GC, HCQ, IMM or combinations</td>
<td>MMF</td>
<td>RTX or BLM</td>
<td>N/A</td>
<td>N/A</td>
<td>60</td>
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<tr>
<td>Non-erosive, non deforming polyarthritis</td>
<td>HCQ +/- HCQ</td>
<td>MTX</td>
<td>RTX</td>
<td></td>
<td>NSAIDs</td>
<td>80</td>
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<tr>
<td>Lupus pericarditis</td>
<td>GC +/- HCQ</td>
<td>MMF, AZA, MTX</td>
<td>RTX or BLM</td>
<td></td>
<td>Pericardiocentesis</td>
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<tr>
<td>Discoid Lupus erythematosus</td>
<td>HCQ +/- GC</td>
<td>Add AZA</td>
<td>MMF or MTX</td>
<td></td>
<td>Sunscreen + topical steroids</td>
<td>70</td>
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<tr>
<td>Lupus ILD</td>
<td>GC + MMF or IV CYC</td>
<td>RTX or IVIG</td>
<td>N/A</td>
<td>AZA or MMF</td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>GC +/- HCQ</td>
<td>Add AZA or MMF</td>
<td>Add RTX, or IV CYC or IVIG</td>
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<td>Splenectomy</td>
<td>50</td>
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<tr>
<td>Uncomplicated digital/cutaneous vasculitits</td>
<td>GC +/- HCQ +/ - MTX</td>
<td>AZA or MMF</td>
<td>IV CYC</td>
<td></td>
<td></td>
<td>80</td>
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Best Practices for Giant Cell Arteritis
Giant Cell Arteritis

- Most common primary systemic vasculitis 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.
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%

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 Guidelines
  - Suggested 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 studies 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?