THE MYRIAD OF AUTOIMMUNE MEDICATIONS FROM A PRIMARY CARE PERSPECTIVE

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Objectives

1. Review briefly the immunology of RA, Lupus, Seronegative arthritis & and wherein drugs have their mechanism of action
2. Review the risks/benefit ratios of medications
3. Outline Primary Care role in managing these diseases
DMARDS for Autoimmune Diseases

- Hydroxychloroquine (Plaquenil)
- Methotrexate (Rheumatrex)
- Sulfasalazine (Asulfadine)
- Azathioprine (Imuran)
- Leflunamide (Arava)
- Mycophenylate Mofetile (CellCept)
- ? Tetracycline (Minocycline, Doxycycline)
- ? Prednisone
ANA & RF Testing

- Consider the pre-test likelihood - if low do not order the test as most likely a + test = false +
- Check ANA if patient has rash, photosensitivity, inflammatory sounding joint pain (back pain, OA knee does not count), Raynauds, Alopecia, Serositis Sicca symptoms etc.
- If ANA screen is + check titer - if 1:40 or less = negative
- Check RF if patient has inflammatory joint pains, especially small joints hands and feet, symmetric, nodules
- If RF + check anti-CCP antibody, ESR and CRP
- Remember obesity causes elevations in CRP and ESR

Case 1a

- 21 yo female college student c/o fatigue, facial rash, hair loss, low grade fevers, joint pain, stiffness and swelling, chest pain w/ deep breathing. + Raynauds, No PPT events or risk behaviors prior to symptoms

- Exam: p=100, 150/90, T-100. Skin- Malar rash, lungs ?faint rub, joints slight synovitis knees

- Labs: WBC 3.2, Hg 10, Plt 150K, Creat 1.0 ANA 1:160, C3 & C4 nl, dsDNA nl
Case 1a

- What is the Diagnosis?
- What other tests are needed?
- What medications do you start as PCP?
Case 1a

- What is the Diagnosis?
  - Systemic Lupus Erythematosus - Mild?
- What other tests are needed?
  - UA no protein, no WBCs and RBCs
  - CXR
  - Echo
- What medications can you start as PCP?
Medication options for SLE

- NSAIDs- Symptomatic
- Prednisone
  - What dose?
- Plaquenil (Hydroxychloroquine)  
  - Mild
- Methotrexate  
  - Moderate to Severe
- Imuran
- Cell Cept
- Benlysta
- Cytoxan
Hydroxychloroquine (Plaquesnil)

- Anti-malarial with immune modulating effects
- Very Long Half Life – takes up to 2-3 months to kick in and to get removed from body
- **Check G6PD prior** - if low do not use
- **Dose:** < 6.5mg/kg ideal body weight
  1. Generally 200mg bid for 6-12 months then 200mg daily thereafter
  2. Adjust dose for renal insuff

Plaquenil & Ocular Toxicity

- Antimalarials bind to melanin in pigmented layer of retina - may damage rods and cones
- Study of 3995 pts on PLQ ocular toxicity rare in 1st 5 years (0.3%); up to 3% in use 20+ years or use >1,000grams (1)

Hydroxychloroquine (Plaquenil) Toxicity

**Toxicity**

1. GI - Nausea
2. Ocular toxicity – Rare,
3. Skin - Allergic rash, Hyperpigmentation
4. Neurologic - Balance, myopathy - rare

**Monitoring**

1. Take w/ food, ½ dose
2. Eye exam every 12 months, keep dose < 6.5mg/kg ideal body weight
3. Caution - sulfa allergic pt
4. Be aware of toxicity, Can overdose so keep away from children
Case 1b

- 21 yo female college student c/o fatigue, rash, hair loss, low grade fevers, joint pain, stiffness and swelling, chest pain w/ deep breathing. No PPT events or risk behaviors

- Exam: p=100, 150/90, T-100. Skin- Malar rash, lungs ?faint rub, joints slight synovitis knees

- Labs: WBC 3.2, Hg 10, Plt 120K, Creat 1.0
  ANA 1:160, C3 & C4 low, dsDNA 250 (nl <20), UA 3+ Protein, + WBC and RBCs

- CXR no effusion
Case 1b

- What is the Diagnosis?
- What other tests are needed?
- What medications do you start as PCP?
Case 1b

- What is the Diagnosis?
  - SLE - moderate - severe

- What other tests are needed?
  - 24 hour urine protein, possible renal biopsy

- What medications can you start as PCP?
  - Patient should be on steroids, maybe Plaquinil
  - Rheumatology input needed
    - CellCept, MTX, Imuran
    - Possible Benlysta
Autoimmunity in Lupus

**Normal Immune System**

- **Normal B Cell**: This type of white blood cell produces antibodies
- **Antibody**: Antibodies attach themselves to germs and try to control or destroy them
- **BLyS**: B Lymphocyte Stimulator (BLyS) is a protein that helps some cells grow
- **Healthy body tissue**
- **Germs**: Viruses, bacteria, and other invaders

**Abnormal Immune System**

- **Autoreactive B Cell**: These are the “bad” version of B cells that make harmful autoantibodies
- **Autoantibody**: While antibodies protect the body, autoantibodies work against the body
- **Chemicals that cause inflammation**
- **Inflamed body tissue**: A sign of lupus disease activity

Google Images-
Immunologic effects of Belimumab (Benlysta)

Systemic Lupus Erythematosus
ADVERSE REACTIONS OCCURRING IN AT LEAST 3% OF PATIENTS AND AT LEAST 1% MORE FREQUENTLY IN PATIENTS TREATED WITH BENLYSTA + STANDARD THERAPY VS PLACEBO + STANDARD THERAPY

<table>
<thead>
<tr>
<th>ADVERSE REACTIONS†</th>
<th>BENLYSTA 10 mg/kg</th>
<th>PLACEBO</th>
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<tbody>
<tr>
<td></td>
<td>+ STANDARD THERAPY</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=674)</td>
<td>(%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
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<td>7</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Depression</td>
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<td>4</td>
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<tr>
<td>Migraine</td>
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<td>Cystitis</td>
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</tr>
<tr>
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<td>2</td>
</tr>
<tr>
<td>Gastroenteritis viral</td>
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</table>
Benlysta Toxicity & Monitoring

**Toxicity**
- GI symptoms
- Infections (Rare)
- Malignancy risks

**Monitoring**
- Rare
- Stop for infections
- Monitor for Cocci, TB, other infections and treat
- Avoid live viruses
Case 2a

- 34 yo female 3 mo post partum c/o worsening joint pains x2 months w/o PPT event, infection, new med
  - MCPs, PIPs, Wrists, Knees, Ankles, Ball of feet
- Having difficulty feeding baby, 1 hour morning stiffness and gelling
- No c/o rash, Raynauds, Serositis, Neurologic Sx
- EXAM: Obese, No rash, ? Synovits vs puffiness in above joints, exam o/w.
- LAB: RF 12 (nl < 13.9), CCP negative, ANA negative, ESR 35, CRP 15
Case 2a

- What is the Diagnosis?
- What other tests are needed?
- What medications do you start as PCP?
Case 2a

- What is the Diagnosis?
  - Seronegative Rheumatoid Arthritis?
  - ANA Negative Lupus?
  - Spondyloarthropathy?
  - Gout?

- What other tests are needed?
  - Maybe HLA B27, Baseline Xrays

- What medications can you – PCP -start?
Medication options
Seronegative RA

- NSAIDs- Symptomatic
- Prednisone
  - What dose – 10mg/d or less
- Plaquenil (Hydroxychloroquine)
- Other-Sulfasalazine, Doxycycline
- Methotrexate
- ? Biologics
Case 2b

- 24 yo female 3 mo post partum c/o joint pains x 2 mo w/o PPT event, infection, new med
  - MCPs, PIPs, Wrists, Knees, Ankles, Ball of feet
- Having difficulty feeding baby, 1 hour morning stiffness and gelling
- No rash, Raynauds, Serositis, Neurologic Sx
- EXAM: Synovitsits in above joints o/w neg.
- LAB: RF 75, CCP > 250, ANA negative, ESR 40, CRP 20
Case 2b

- What is the Diagnosis?
- What other tests are needed?
- What medications do you start as PCP?
Case 2b

- What is the Diagnosis?
  - Seropositive Rheumatoid Arthritis
  - ANA Negative Lupus? NO rare

- What other tests are needed?
  - Baseline Xrays, Hepatitis screen, PPD, CXR

- What medications do you –PCP start?

- Refer to Rheumatology
DMARDS for Autoimmune Diseases

- Hydroxychloroquine (Plaquenil)
- Methotrexate (Rheumatrex)
- Sulfasalazine (Asulfadine)
- Azathioprine (Imuran)
- Leflunamide (Arava)
- Mycophenylate Mofetile (CellCept)
- Tetracycline (Minocycline, Doxycycline)
- Prednisone
Arthritis Still Progressed
Biologics for Arthritis

- Enbrel
- Humira
- Cimzia*
- Simponi
- Anakinra
- Orencia
- Reicade
- Actemra
- Rituxan*
- Benlysa-Lupus

Self Administered shots
* Can get in clinic

Intravenous in clinic every 1-2 months
*every 4-6 mo
Immunology of autoimmune diseases is very complicated

Iain B. McInnes & Georg Schett
Nature Reviews Immunology 7, 429-442 (June 2007)
Medications for more aggressive RA

- **Prednisone**?
  - 10mg/d or less
  - Kenalog 40mg IM

- **DMARDs**-
  - Hydroxychloroquine (Plaquenil)- OK to start but likely will need stronger medication
  - Methotrexate
  - Arava (Leflunamide)
  - Sulfasalazine

- **Biologic**?
  - Some literature supports starting Biologics for strong + CCP

Moderate to severe RA
Methotrexate

- Stronger Immune Suppression
  - Dihydroflolate reductase inhibitor
  - Inhibits cell division- inhibits purine and Pyrimidin synthesis
- Starting med for most Rheumatologists-especially if anti-CCP +
- Check baseline labs: CBC, CMP and Hepatitis Panel, pregnancy test young females
Methotrexate Dosing

- Weekly Medication
  - Start 3 tabs/wk @ 2.5mg/tab = 7.5mg/wk
  - Usually raise by 1 tab every 2-4 weeks based on adverse events and effectiveness
  - 6-10 tabs/wk average dose (15-25mg/wk)
  - Sub q for GI intolerant

- Folic Acid 1mg/d
- Nsaids may affect clearance
# Methotrexate Toxicity

## Toxicity
1. Hepatic
2. Pulmonary
3. Lymphoma, marrow suppression
4. GI, flu-like symptoms, alopecia

## Monitoring
1. Hepatitis screen baseline,
   - LFts every 2-3 mo, no etoh
2. Sx & Lung exam every visit (q4mo)
3. Monitor Sx, CBC, lymph exam q 3-4mo
4. Decrease dose, change to sub q
Biologics for Arthritis

- Enbrel
- Humira
- Cimzia*
- Simponi
- Anakinra
- Orencia
- Remicade
- Actemra
- Rituxan**
- Benlysa-Lupus

Self Administered shots
* Can get in clinic

Intravenous in clinic
every 1-2 months
**every 4-6 mo
Biologics-General

Extrapolation from numerous biologic clinical trials
Primary care role in RA patients on biologics

- Stop for infections
- Low threshold to treat infections
- Yearly CXR, TB testing (quanteferon)
- Vaccinations-
  - killed only unless hold medication
  - Live virus vaccine- 6 weeks pre and post biologics
- Cancer screening
  - Lymphoma- monitor adenopathy, weight
  - Skin cancer, Routine screening
- Monitor for Neurologic Sx, Autoimmune Ds
Case 3

- 54 yo female c/u joint pains wrist, hands and knees; sicca symptoms, some DOE o/w no rashes or other systemic symptoms
- **Exam:** 175#, Parotid fullness, dry oral; mucosa, Faint basilar rales, RRR w/o M,R,G, mild synovitis hands, wrists and ankles
- **Labs:** CBC nl, Renal, LFts Ok, ESR 75, UA trace protein, ANA + 1: 1280 speckled, RF + 340, Polyclonal gamopathy
Case 3

- What is the Diagnosis?
- What other tests are needed?
- What medications do you start as PCP?
Case 3

- What is the Diagnosis?
  - Lupus
  - Rheumatoid Arthritis
  - Sjogren’s Syndrome

- What other tests are needed?
  - SSA and SSB = Sjogren’s antibodies
  - Possible pulmonary evaluation

- What medications can you start as PCP?
Sjogren’s Syndrome Treatment

- Immune Modulation
  - Plaquenil, MTX, Rituxan

- Sicca Symptoms
  - Artificial Tears, Saliva
  - Restasis (Cyclosporin) eye drops
  - Salagen (Pilocarpine) 5mg qid
  - Evoxac (Cevemaline) 30mg tid
Case 4

- 34 yo male w/ 6 mo Hx progressively worsening low back pain, worse in the morning & better as he moves around; denies inflammatory eye symptoms, urethritis, rash
- Exam: Tenderness SI joints bilat, Schoeber’s deceased 4cm, occipute to wall 1cm, chest expansion decreased; decreased motion hips
- Labs, Mild anemia, CMP Ok, ESR 50, CRP 20, RF and ANA negative
Case 4

- What is the Diagnosis?
- What other tests are needed?
- What medications do you start as PCP?
Case 4

- What is the Diagnosis?
  - Seronegative RA
  - Seronegative spondyloarthropathy

- What other tests are needed?
  - ? HLA B27, LS spine w. SI views, ? MRI SI joints, Hip Xrays

- What medications can you start as PCP?
Seronegative (AS, PA) Spondyloarthritis

- NSAIDs (Indomethacin)
- Hydroxychloroquine (Plaquinil)
- Sulfasalazine (SSA)
- Biologics
  - Enbrel
  - Humira
  - Simponi
  - Remicade
Case 5a

- 65 yo male w/ intermittent abrupt onset painful swelling joints- right wrist but in the last 2 years similar sx left wrist, knees and ankles; no PPT event, trauma or meds.
- Exam: slight synovitis wrists right > left, MCps index and long bilaterally
- Labs CBC, Renal, nl, ESR and CRP nl, transaminases mildly elevated
Xrays showing CPPD Deposition

Radiographic changes c/w pseudogout
Case 5a

- What is the Diagnosis?
- What other tests are needed?
- What medications do you start as PCP?
Case 5a

- **What is the Diagnosis?**
  - Seronegative RA
  - Pseudogout vs gout vs other crystalline arthritis

- **What other tests are needed?**
  - X-Rays hands and knees - chondrocalcinosis, secondary DJD, uric acid when not flaring

- **What medications can you start as PCP?**
  - NSAIDS (must monitor renal)
  - Prednisone taper starting 20mg/d for flare
  - Plaquenil – pseudogout
Case 5b

- 65 yo male w/ intermittent abrupt onset painful swelling joints- right wrist but in the last 2 years similar sx left wrist, knees and ankles; no PPT event, trauma or meds.
- Exam: slight synovitis wrists right > left, swelling in several MCps DIPs asymmetric, nodules noted and some changes in his toes
- Labs CBC, Renal, nl, ESR and CRP nl, transaminases mildly elevated
Case 5b

- Xrays show no condrocalcinosis
- Exam suggests tophi

Gouty Tophi of the distal interphalangeal joints of the toes
Case 5b

- What is the Diagnosis?
- What other tests are needed?
- What medications do you start as PCP?
Case 5b

- What is the Diagnosis?
  - Gout

- What other tests are needed?
  - Uric Acid when not flaring
  - Aspirate tophus or joint

- What medications do you start as PCP?
  - Colcrys or nsaids to prevent flare
  - Allopurinol or Uloric to lower Uric Acid
  - Low Purine, Low fructose diet, Increase Vitamin C
Summary

- Immunology of autoimmune disease complicated
- Medications target specific areas of the immune system- so can cause immune suppression in addition to other toxicities
- Proper diagnosis is essential (eg. no TNF inhibitors w/ Lupus)
- PCP can initiate some disease modifying meds if comfortable monitoring/managing toxicity
- PCP and Rheumatologist must work together to monitor toxicity and safely use medications
Medication Choice

Risks

Benefits