Update in Rheumatology 2015

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• I receive grant funds from NIH.
• I have no conflicts to disclose.
Road map

• RA: Can we de-escalate therapy in patients in remission?
• Psoriatic arthritis: 1L-23 inhibitors, 1L-17 inhibitors, phosphodiesterase 4 inhibitors, CVD risk
• ANCA vasculitis: new treatment options
• Polymyalgia Rheumatic treatment guidelines
• Quick Pearls
# Rheumatic Disease in US

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
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</thead>
<tbody>
<tr>
<td>Osteoarthritis</td>
<td>15,800,000</td>
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<tr>
<td>RA</td>
<td>2,100,000</td>
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<tr>
<td>Gout</td>
<td>1,000,000</td>
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<tr>
<td>AS</td>
<td>318,000</td>
</tr>
<tr>
<td>Psoriatic Arthritis</td>
<td>160,000</td>
</tr>
<tr>
<td>SLE</td>
<td>131,000</td>
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<tr>
<td>JRA</td>
<td>71,000</td>
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</tbody>
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Rheumatoid Arthritis

Early Disease

Late Disease
RA Epidemiology

- Affects all ages
- Peaks in 40s to 60s
- 50% of patients diagnosed with RA will not be in the workforce in 10 years
- Women affected 2-4 times more than men
- More prevalent in Native American and Caucasian populations
The Burden of Rheumatoid Arthritis

• Systemic inflammatory disease\(^1\)
• Autoimmune etiology\(^1\)
• Prevalence 1\% in varied ethnic groups
  • 2 million people in the United States\(^1\)
• Lifetime cost approaches that of cardiovascular diseases\(^2\)
• Associated with an increased mortality risk\(^3\)

Survival of Patients With Severe Rheumatoid Arthritis

*Defined as >20 actively inflamed joints.

Adapted with permission from Pincus et al. Ann Intern Med. 1999;131:768.
Treatment Pyramid for RA: Treat Aggressively Early

- Surgery
- Change Biologic
- Add anti-TNFα or other biologic
- Add or substitute drugs: Leflunomide
- Multiple DMARDs: SSZ, HCQ, MTX, Prednisone

Approved Drugs for RA

**Oral DMRADS**
- Sulfasalazine
- Hydroxychloroquine
- Methotrexate
- Leflunomide
- Azathioprine
- Cyclosporin

**TNF antagonists**
- Adalimumab
- Etanercept
- Infliximab
- Golimumab
- Certolizumab pegol

**IL-6 antagonists**
- Tocilizumab

**JAK inhibitors**
- Tofacitinib

**T cell inhibitor**
- Abatacept

**B-cell depletion**
- Rituximab

**IL-1 antagonist**
- Anakinra
Can We Sustain RA Remission and Taper DMARDs?

Half-dose Anti-TNF plus MTX is more effective for maintaining remission than MTX.

Emery et al., NEJM 2014; 371:1781-92
Psoriatic Arthritis
Update in Therapies
Psoriatic Arthritis (PsA)

- Men=Women
- Age of onset peaks in 4th and 5th decades
- Prevalence 1-2/1000 and 10-30% of Psoriasis patients
- Often seen with nail pitting, nail onycholysis, scalp or intergluteal lesions
- No association with severity of skin and risk of arthritis
- Associated with HLA-B27
Role of IL-17 in the Pathogenesis of Psoriasis
Drug Targets in the Pathogenesis of Psoriasis

- Anti-TNFα
  - Etanercept
  - Adalimumab
  - Infliximab
  - Golimumab
  - Certolizumab

- Anti-IL-12/23
  - Ustekinumab

- Anti-IL-17
  - Secukinumab

- Anti-PDE4
  - Apremilast
Secukinumab (Stelara)
• Anti-IL 17 Receptor A
• Subcutaneous injections
  • 1 per week for 4 weeks then q4weeks
• Side effects: infection, TB, non-melanoma skin cancer

McInnis et al. Lancet, 2015
Brodalumab for psoriatic arthritis

- Brodalumab
  - Anti-IL-17 Receptor A
  - Subcutaneous q2 weeks

- Side effects:
  - Infections
  - Neutropenia

Mease et al. NEJM 2014:2295-2306
Apremilast for Psoriatic Arthritis

Apremilast (Otezla)

- Phosphodiesterase 4 (PDE4) inhibitor
  - 30mg orally BID (titrated up from 10mg BID)
  - Serious side effects:
    - Weight loss (5-10% body mass)
    - Depression
    - Suicides

![Graph showing ACR20 response in overall population and biologic experience.](image)

Psoriatic Arthritis Treatment Scheme

Psoriatic Arthritis

Skin & Nails
- Oral DMARDs (MTX, SSZ, HCQ, CSA, Leflunomide, AZA)
- Anti-TNFα
  - Ustekinumab
  - Apremilast
  - Secukinumab

Peripheral Arthritis
- NSAIDS
- Anti-TNFα

Axial Arthritis
- NSAIDS
- Oral DMARDs
- Anti-TNFα
  - Ustekinumab
  - Apremilast
  - Secukinumab

Enthesitis

Dactylitis
- NSAIDS
- Anti-TNFα
  - Ustekinumab
  - Apremilast
  - Secukinumab

No Oral DMARDs
Cardiovascular Disease Develops Earlier in Psoriatic Arthritis, Psoriasis, and RA

Patient Numbers
PsA: 8,706
PsO: 138,424
RA: 41,752
Con: 81,573

PsA and Cardiovascular Disease

- Increased risk of CV death (RR 1.61, 95%CI 1.09-2.38)
- Dyslipidemia that worsens with active disease (↓HDL and ↑TG)
- 30% with hypertension
- Obesity, metabolic syndrome, and diabetes are increased
- Increased metabolic syndrome compared to RA [OR 2.44 (95%CI 1.48-4.01)]
- **Metabolic syndrome improves with anti-TNF therapy compared to methotrexate alone**

Ogdie et al. J. Rheumatol 2014; 41:2315-2322
Costa et al., Clin Rheumatol 2014; 33:833-839
ANCA Vasculitis

Update in Treatments
ANCA-Associated Vasculitis

- Granulomatosis with polyangiitis (GPA) = Wegener's granulomatosis
- Microscopic polyangiitis (MPA)
- Eosinophilic granulomatosis with polyangiitis (EGPA) = Churg-Strauss syndrome

Orbital pseudotumor  
Palate perforation  
Palpable purpura  
Crescentic necrotizing glomerulonephritis
Rituximab is Effective for Inducing Remission of ANCA-Associated Vasculitis

- **Rituximab** (anti-B cell antibody) versus oral cytoxan
- **RAVE study**: double-blinded placebo controlled trial comparing rituximab (375gm/m2 IV weekly for 4 weeks) to cytoxan (2mg/kg per day orally)
  - 99 pt assigned to rituximab and 98 to cytoxan
  - Rituximab was non-inferior to cytoxan with remission in
    - 63% Rituximab vs 53% cytoxan
  - Was superior to cytoxan in severe cases with 67% remission vs 42% with cytoxan
  - Rituximab had fewer adverse events (19% vs 32%)

Stone JH et al., NEJM 2010; 363:221-232
Does Rituximab or Azathioprine Maintain ANCA-Vasculitis Remission Better?

Rituximab Maintains Remission Better than Azathioprine

All patients in remission with Cytoxan and glucocorticoids Randomly assigned to Rituximab 500mg at 0 and 2 weeks then q 6months versus Azathioprine
ANCA-Vasculitis Treatment

Ntatsaki et al. Rheumatology 2014
PMR

Updated Treatment Guidelines
Polymyalgia Rheumatica: Symptoms

- Pain and morning stiffness:
  - Shoulder and pelvic girdle, arms, thighs, low back
  - Symmetrical involvement
- May have mild synovitis
- Low grade fever
- Weight loss/anorexia
- Fatigue
- Screen for temporal arteritis symptoms
- Age>50
- ESR>50
- Shoulder/pelvic pain (no true weakness)
Polymyalgia Rheumatica: Epidemiology

- **Age:** >50
  - Increased incidence with increased age, peaks at 70
  - Approaches 1% in the elderly
- **Increased in northern European ancestry**
- **Female: male ratio is 2:1**
- **Elderly, Caucasian female smokers are highest risk**
New PMR Treatment Guidelines

- Prefer glucocorticoids to NSAIDS
- Don’t treat with >30mg a day
- Most patients will need treatment for 1-3 years

PMR

Prednisone 12.5-25mg daily

Clinical response at 4 wks

Good

Taper prednisone to 10mg by 8 wks

Remission

If severe, with synovitis, or unable to take prednisone add Methotrexate 7.5-10mg weekly

Increase prednisone back to pre-flare dose

Relapse

Methotrexate 7.5-10mg/wk

Taper Prednisone more slowly 1mg/2month

Remission

Taper therapy

Arth & Rheum 2015, 67:2569-2580
Quick Pearls
DPP-4 Inhibitors may cause severe joint pain and swelling

- Dipeptidyl peptidase-4 inhibitors:
  - Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Tradjenta), and Alogliptin (Nesina)
- Joint pains may occur 1 day to years after starting drug
- May mimic new onset rheumatoid arthritis with morning stiffness, swelling, and tenderness
- Arthralgia and myalgia may lead to hospitalization
- Symptoms typically resolve within a month after discontinuation of drug
- Challenge with another DPP-4 may cause recurrence

Epidural Corticosteroids for Radiculopathy and Spinal Stenosis has Minor Benefits

- 400 patients randomized to epidural injections with lidocaine vs lidocaine and glucocorticoids
  - At 6 wks, both groups had similar improvement in pain and function
  - The GC group had more adverse events than lidocaine only

- Meta-analysis of 38 placebo controlled trials
  - Immediate pain reduction was seen with GC compared to control injection
  - Benefits were small and not sustained
  - There was no effect on long-term surgery risk

Friedly JL et al., NEJM 2014; 371:11-21
Chou et al., Ann Int Med 2015; 163:373-381
Scleroderma and Rituximab
European Scleroderma Trial and Research (EUSTAR)

• 63 scleroderma (46 diffuse, 17 limited)
• Rituximab 1000mg IV week 0 and 2 compared to 25 matched controls

Thank you!