Rheumatoid Arthritis

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No disclosures

This is an evidence based medicine talk.

Objectives

• Better diagnose rheumatoid arthritis, especially early disease
• Know the most common differential diagnosis for a positive rheumatoid factor
• Understand screening, monitoring, and common side effects of DMARD and biologic treatment
• Recognize comorbidities associated with rheumatoid arthritis and its treatment

What is Rheumatoid Arthritis?

• Symmetric, inflammatory, peripheral polyarthritis
• Synovial proliferation and inflammation leading to deformity and erosions.

Epidemiology

• Most prevalent chronic inflammatory joint disease
• Affects 0.5-1% of European and North American Adults with considerable variation.
  – Absent in parts of Africa
  – N. America has highest rates of disease
  – Native Americans: Up to 5% are affected
• Female: Male is 3:1
• The incidence increases with age in most populations until about the 8th decade of life, when it declines.

Risk Factors

• Genetic: HLA-DRB1
  – Shared Epitope
• Tends to “cluster” in families
• Environmental
  – Smoking
    • Most important environmental risk factor
  – Bacteria: P. gingivalis and Proteus
    • Induce citrullination
    • Molecular mimicry
Diagnosis

- Diagnosis
  - Combination of clinical findings, lab tests, and imaging.
- Heterogeneous
  - Gradual, insidious onset → most common
    - One or a couple of joints to develop into the classic symmetrical disease.
  - Acute onset with fever, polyarthritis, and extra-articular manifestations.
  - Some patients present with PMR type picture then develop synovitis
- Pain, Swelling, and Stiffness
  - Redness, warmth are less common
  - Tenosynovitis, bursitis, and carpal tunnel may be present

Articular Manifestations

- Typical joint involvement at onset
  - PIP, MCP, wrist, and MTP joints.
  - Shoulder, Hip → rare at disease onset
  - C-Spine disease is common but later in disease
    - All patients with RA need neck films prior to surgery
- Soft tissue swelling, tenderness
  - “Boggy” feeling to the joint.
- Limited motion
- Detection of synovitis is essential for the diagnosis

Laboratory Data

- Synovial Fluid Analysis:
  - Should it be done?
    - If there is the possibility of gout...gout can be really sneaky.
  - What can be learned from synovial analysis?
    - Cell count, gram stain, culture and microscopic examination for crystals.
    - Fluid will be inflammatory
      - > 1,500 WBCs

Laboratory Data Continued

- ESR and/or CRP elevation
- Thrombocytosis, Leukocytosis
- Leukopenia → This is not a typical feature.
  - Felty’s: Neutropenia, Splenomegaly
  - LGL (large granular lymphocyte leukemia)
  - Treat the underlying disease.
    - I usually send flow cytometry before initiating therapy.
- Mild inflammatory anemia
- Hypergammaglobulinemia
Laboratory Data Continued

• Rheumatoid Factor and anti-CCP antibodies
  – 70-80% of RA patients
  – 20-30% of RA patients are seronegative.
  – Useful for confirming clinical impression
  – Both RF and anti-CCP can be present up to 10 years prior to disease.

• ANA in appropriate situations
  – Mildly elevated ANA can be seen in RA and is of no clinical significance.

Anti-Cyclic Citrullinated Peptide Antibodies

• Antibodies against citrullinated residues of proteins
  – Specificity is 95% for RA, Sensitivity 70%
  – 35% of RF negative patients at presentation will be anti-CCP positive.
  – Negative in patients with +RF w/o RA

Rheumatoid Factor

• IgG, IgM, or IgA targeting the Fc-part of IgG
  – IgM-RF is most common

Imaging

• Plain x-rays are gold standard for diagnosis joint damage.
  – Absence of erosions doesn’t r/o RA.
  – Hand and foot films are usually obtained for baseline.
  – Periarticular osteopenia can be an early finding.
    • Seldom mentioned by reading radiologist.
• Ultrasound and MRI
  – Pick-up early disease/subclinical synovitis.

Diagnosis: ACR 2010 Criteria

• 1987 Criteria: Outdated and poor for early disease
Diagnosis: ACR 2010 Criteria

- Number and site of involved joints
  - 2 to 10 large joints = 1 point
  - 1 to 3 small joints = 2 points
  - 4 to 10 small joints = 3 points
  - Greater than 10 joints (including at least 1 small joint) = 5 points
- Serological abnormality (RF/anti-CCP)
  - Low positive (above the upper limit of normal [ULN]) = 2 points
  - High positive (greater than three times the ULN) = 3 points
- Elevated acute phase response (ESR/CRP) above the ULN = 1 point
- Symptom duration at least six weeks = 1 point
- Total score of at least 6

Example: Synovitis in 2 MCPs, elevated ESR, low positive anti-CCP, symptoms for 8 weeks

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Differential Diagnosis

- Acute Viral Polyarthritis: Can trick you!
  - ParvoB19
  - Hepatitis B, Hepatitis C
  - Chikungunya
- Hypermobility and FMS: arthralgias, not arthritis
- Reactive Arthritis
- Lyme: Appropriate travel history. Intermittent or persistent inflammatory arthritis of a few large joints. NOT arthralgias.
- Psoriatic arthritis: more oligoarticular at onset
  - Can be hard to distinguish absence of Psoriasis. First degree relative counts. Look at nails (pits are early sign) and onychodystrophy
- Crystal arthritis: can become chronic and assume polyarticular distribution
- Infectious: Monoarticular. Can be polyarticular in immunocompromised.
- Sacroili: Always think about sacroiliac mono-arthritis.

Treatment

- There are a lot of treatment options!
- Goal is EARLY, aggressive treatment to control symptoms and damage.
- Combination treatment is frequently needed
- NSAIDs
  - Not very effective
  - Toxicity

What is a DMARD?

- Drug used in the therapy of inflammatory joint diseases (RA, JIA, PsA, and AS)
- Slow onset of action for an effect
- Effect on the acute phase reactants
- Improvement in the functional status
- Slow down the rate of radiologic progression of the disease
- All have increased risk of infection
FDA Approved DMARDs

• **Traditional DMARDs**
  - Corticosteroids
  - Hydroxychloroquine
  - Methotrexate
  - Sulfasalazine
  - Leflunomide
  - Azathioprine
  - Auranofin/Gold
  - Cyclosporine
  - Penicillamine
  - ASA

• **Biologic Agents**
  - Etanercept (Enbrel)
  - Infliximab (Remicade)
  - Adalimumab (Humira)
  - Certolizumab (Cimzia)
  - Golimumab (Simponi)
  - Tocilizumab (Actemra)
  - Abatacept (Orencia)
  - Anakinra (Kineret)
  - Rituximab (Rituxan)
  - Tofacitinib (Xeljanz)

Laboratory testing prior to initiating DMARD treatment

• CBC and CMP
• Hepatitis B and C Studies
  - All DMARDs except Prednisone, Hydroxychloroquine
  - Don’t forget to Hepatitis B core antibody
  - Patients with + Hepatitis B core antibody, surface antibody + or – are at risk for reactivation with immunosuppression.
  - Hepatology consults is needed in patients with + surface antigen
• Chest X-Ray
  - Methotrexate
• PPD/Interferon release assay
  - Biologics, Leflunomide

Low Dose Prednisone

• Prednisone
  - Usually given at 10 mg daily or 5 mg BID
  - Quickest acting. Helps people go back to work.
  - Good data on low dose prednisone on clinical improvement, less need for NSAIDs, less bone erosions and joint space narrowing.
    - Considered a DMARD in early RA
  - Goal—slow taper to get to the lowest dose that controls disease as you ramp up traditional DMARDs

Prednisone

• FDA approval 1950
• No defined guidelines for indications or dosages
• No understanding of mechanism of action or pharmacology
• Era of empiricism and the dominance of clinical impression in Medicine
• SO—physicians used glucocorticoids in whatever diseases they deemed necessary, any dose, and frequently for too long. HAS THIS CHANGED?

Prednisone inclusion in MTX-based tight control strategy for early RA

• Monitor T&S joint count, VAS-general, ESR, adjust treatment to reach 20% improvement each visit—2 yr.

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<th>MTX + Placebo</th>
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Similar Effects of DMARDs, Glucocorticoids and Biologics on X-Ray Progression in RA

- Meta analysis of 70 randomized studies
- Combination of 2 DMARDs better than one
- Glucocorticoids with any DMARD better than DMARD alone
- Two DMARDs plus GC equal to Biologic plus MTX

Graudal, N. and Jurgens, G. Arth and Rheum October 2010, pp 2852-2863

Prednisone

- Association with infections in chronic RA patients over 65 on prednisone > 8 mg/d
- Patients with chronic RA with high DAS have decreased life span influenced by prednisone > 7.5 mg/d

Prednisone

- Studies published are of single daily doses of 5, 7.5, or 10 mg per day given in morning are known effective.
- Known anti-inflammatory effect from a dose of 5 or 7.5 mg is maximum at 5+ hours and less by 24 hours
- Would similar low doses given every 12 hours (with a dose qhs), 5 mg bid----or 2.5 mg bid, be even more effective and equally safe?
  - That has been the practice at Mayo since the early 1950’s and is the practice at Grady/Emory

Prednisone

- Active and especially early RA with active inflammation in many joints
- Dose—usually prednisone 5-10 mg per day, preferred---5 mg bid as starting dose
- Duration—when inflammation controlled, slow taper (decrements of 1 mg-2.5 mg every two week-month) to the lowest dose that controls inflammation with a goal of 5 mg or less per day.

Hydroxychloroquine

- Hydroxychloroquine (Plaquenil)
  - Mild, seronegative disease
  - 200-400 mg daily based on weight
  - Adjunct to MTX
  - Triple Therapy (MTX, Sulfasalazine, Plaquenil)
  - Very few toxicities. Eye exams
  - Safe to use in Hepatitis B and C

Diurnal pattern of glucocorticoid secretion: Low early am, peaking later am and resulting in more RA joint pain and stiffness in early am.
Methotrexate: Anchor Drug in RA

• Given weekly with daily folic acid.
• Titrate up from 7.5-10 mg to 20 mg weekly based on clinical response. PO or SC
• SE: oral sores, GI upset, alopecia, acute pneumonitis, liver fibrosis
• CXR prior to therapy
• Lab monitoring (CBC, CMP) monthly x 3 then q3months (minimum).
• Contraindicated: liver disease, excessive alcohol intake, contemplating pregnancy, or severe renal impairment (GFR< 30 mL/min)
• Teratogen: must be off for 3 months prior to conception (males included)

Leflunomide (Arava)

• Similar efficacy to MTX
  – Non-inferior to MTX, but it’s usually tried after MTX.
• 10-20 mg daily
• AVOID: women of childbearing age/potential
• SE: weight loss, peripheral neuropathy, transaminases elevation, cytopenias, rash, GI upset, weight loss
• Lab monitoring (CBC, CMP) monthly x 3 then q3months(minimum).

Sulfasalazine

• Used mostly in combination with MTX, HCQ
  – 500 mg pills.
    • Dose is 500mg- 1500 mg BID
  – SE: GI upset, rash, myelosuppression, spermatogenesis
  – Lab monitoring (CBC, CMP) monthly x 3 then q3months(minimum).

TNF-alpha inhibitors

• Expensive. Not used first line (rare situations)
• Work best as combination therapy with MTX
• SC: Adalimumab, Etanercept, Certolizumab, and Golimumab.
• IV: Infliximab, Golimumab
• Must screen for TB
• Lab monitoring. No definite guidelines. CBC/CMP every 3-6 months.
• SE: Infections, neutropenia, demyelination, cutaneous reactions (vasculitis, drug induced lupus, psoriasis, and injection site reactions), infusion reactions and induction of autoimmunity, ? heart failure exacerbation, ?malignancy, pulmonary disease, Sarcoid, hepatotoxicity

Triple Therapy is Noninferior to MTX + TNF

• A Randomized Comparative Effectiveness Study of Oral Triple Therapy Versus Etanercept Plus Methotrexate
  • Triple Therapy in Early Active Rheumatoid Arthritis
  • A Randomized, Single-Blind, Controlled Trial Comparing Step-Up and Parallel Treatment Strategies
**My General Approach**

- Polyarticular inflammatory arthritis seen on exam
- Try to aspirate if there’s an effusion.
- Start Prednisone 5 mg BID. If very mild, 2.5 mg BID.
- Order CBC, CMP, ESR, CRP, UA, RF, anti-CCP, and x-rays depending on presentation
  - Depending on presentation/age/sex/ethnicity: ANA, uric acid, HLA-B27

**Responsibility for Vaccination**

- Specialists who care for immunocompromised patients share responsibility with the PCP for ensuring that appropriate vaccinations are administered to immunocompromised patients.

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**Rheumatoid Arthritis and the range of multi-comorbidity**

My General Approach

- Seronegative: Think about etiology a little more.
  - start Plaquenil if mild or Methotrexate

- Seropositive:
  - MTX 10 mg weekly with daily folic acid
  - Taper Prednisone and ramp up MTX to 20 mg weekly based on clinical response
  - If unhappy with prednisone dose:
    - Add Plaquenil
    - Continue to be unhappy: Discuss triple therapy vs anti-TNF therapy
Influenza

- Annual vaccination is recommended for immunocompromised patients aged ≥6 except for patients who are very unlikely to respond, such as those receiving intensive chemotherapy or those who have received anti-B-cell antibodies within 6 months.

IDSA Guidelines for Immunocompromised

Pneumovax

- PPSV23 should be administered to patients aged ≥2 years with chronic inflammatory illnesses with planned initiation of immunosuppression, low-level immunosuppression, and high-level immunosuppression. Patients should receive PPSV23 ≥8 weeks after PCV13, and a second dose of PPSV23 should be given 5 years later.

IDSA Guidelines for Immunocompromised

Prevnar 13

- PCV13 should be administered to adults and children with a chronic inflammatory illness that is being treated with immunosuppression.

IDSA Guidelines for Immunocompromised

Zoster

- Patients with chronic inflammatory disorders who are

- Shingles Vaccine: Bottom Line

  - Consider giving to ALL RA patients >60 y/o
    - many RA patients may ultimately receive biologic agents
  - OK to give if on MTX ≤ 4 mg/kg/week, Sulfasalazine, Azathioprine < 3 mg/kg/day, Leflunomide, or Prednisone <20 mg/day
  - Avoid Zoster in patients actively receiving biologics(TNF inhibitors, Abatacept, Rituximab, etc)
  - Vaccinate 2 weeks prior to starting biologic

IDSA Guidelines for Immunocompromised
Common mechanisms underlying atherosclerosis and rheumatoid arthritis

Cumulative incidence of cardiovascular manifestations in patients with or without RA

Cumulative incidence of cardiovascular event in patients with or without RA

Lipids and Inflammation - The Lipid Paradox

EULAR 2015 recommendation update for cardiovascular risk management in patients with Rheumatoid Arthritis

Additional Considerations

- Low-dose aspirin 81 mg daily to reduce cardiovascular events.
  - Doses of 20-100mg/kg suppress proinflammatory cytokines.
- Blood Pressure control
- Initiate bone protective therapy if using low dose Prednisone.
Renoir and RA

Thank you

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- ACR 2016 session: RA when the patient is well. Understanding and managing multibody. McInnes.