2013 Rheumatoid Arthritis Update
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For your information
- Clinical Professor of Medicine, David Geffen School of Medicine at UCLA
- Private practice, Tustin CA
- Investigator in clinical trials relevant to this lecture including:
  - anti-TNF for Abbott (adalimumab)
  - anti-TNF (etanercept), IL1ra (anakinra) and anti-RANKL (denosumab) for Amgen
  - leflunomide for Aventis (formerly Hoechst Marion Roussel) (301US)
  - Anti-TNF for UCB (certolizumab)
  - Anti-IL-6 for Roche (tocilizumab)
  - Abatacept (Bristol Meyers Squibb)
- Speaker, consultant and/or grant support from companies with products relevant to this lecture including: AbbVie, Amgen, Pfizer, UCB

The Role of the Physician Assistant in the Management of the RA Patient
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Rheumatoid Arthritis
- Rheumatoid arthritis (RA), an autoimmune disease of unknown etiology, is a form of inflammatory arthritis characterized by symmetric, erosive synovitis and, in some patients, systemic involvement
- Epidemiology
  - Peak prevalence between age 55 and 80
  - Prevalence estimated at ~1 to 2%
  - Genetic predisposition
- All cause mortality 60% to 70% higher in RA patients than in patients with OA and no arthritis

Valtonen et al J Rheumatol. 2003;30:1106-12
### Signs and Symptoms

**Articular**
- Polyarticular, often **symmetrical**
- Joint **swelling** and tenderness
- Limitation of motion
- Malalignment of joints
- Pain, often at rest

**Systemic**
- Fever, weight loss, fatigue, anemia
- Morning **stiffness** almost universal

**Extra-articular**
- Rheumatoid nodules
- Vasculitis
- Pulmonary fibrosis
- Ocular disease (sicca, episcleritis)
- Carditis, pericarditis

### 2006 Update

- Joint damage can begin early
- Joint space narrowing (JSN) seen in 83% of patients within the first 2 years of disease
- JSN and erosion are seen in
  - 67% of patients within the first 2 years of disease
  - 70% of patients within the first 5 years of disease
- Radiographic progression
  - is most rapid during the first 5 years of disease
  - begins early and continues over the patient’s lifetime

### Systemic Effects of Cytokines

**Caveat: CV Disease and the RA Patient**

- Watson et al. found vascular events 30% to 60% higher in RA patients than in patients with OA and no arthritis
  - Similar inflammatory and immunological responses in RA and atherosclerosis
    - Abundance of cytokine secreting inflammatory cells in atherosclerotic plaques
    - Presence of acute phase reactants in tissue plaque and peripheral blood
    - Release of TNF, IL1, adhesion molecules, growth factors, and matrix metalloproteinases contribute to inflammatory response
  - Consider increased risk and whether to implement diagnostic and therapeutic measures


Grover S et al. Subclinical atherosclerosis in rheumatoid arthritis in India. J Rheumatol. 2006; 33:244-247

Dessein PH, Joffe BI. When is a patient with rheumatoid arthritis at risk for cardiovascular disease? J Rheumatol. 2006; 33:201-203.

### Clinical Course of RA

- Type 1 = Self-limited—5% to 20%
- Type 2 = Minimally progressive—5% to 20%
- Type 3 = Progressive—60% to 90%

Goals of RA Therapy

• Relieve pain/inflammation
• Retard disease progression
  — Prevent or control joint damage
• Maintain or improve function for activities of daily living and work
  — Prevent or limit work disability
  — Maintain or maximize independence
• Maximize quality of life
• Minimize risks of therapy

The goals are best achieved when RA is diagnosed early and treated aggressively


Establish the Diagnosis of RA

• Patient history and physical examination are critical components in making a diagnosis of RA
  — What are the symptoms?
  — What does an examination of the joints reveal?
    • Symmetric arthritis is classic for RA
• Blood tests are useful to support a diagnosis - not usually independently diagnostic
  — Inflammation may sometimes be detected by laboratory tests, e.g., ESR or “CRP” (quantitative C reactive protein)
  — The presence of a + rheumatoid factor is not specific for - or necessary for - a diagnosis of - RA
• X-rays may show soft tissue swelling, juxta-articular osteopenia, loss of articular cartilage or marginal bone erosions, suggesting RA – hands and feet are preferred

Key Features of RA

• Symptoms >6 weeks’ duration
  — Often lasts the remainder of the patient’s life
  — Disease activity differs in people; patients sometimes have flares, or increased disease activity
• Inflammatory synovitis
  — Palpable synovial swelling
  — Morning stiffness >1 hour, fatigue
• Symmetrical and polyarticular (>3 joints)
  — Typically involves wrist, MCP, PIP, MTP joints
  — Typically spares certain joints
    • Thoracolumbar spine
    • DIPs of the fingers and CMCs in the hands
• May have nodules: subcutaneous or periosteal at pressure points
• Rheumatoid factor (RF)
  — 45% positive in first 6 months
  — 85% positive with established disease
  — Not specific for RA
  — High titer early is a bad sign
• Marginal erosions and joint space narrowing on x-ray

Summary: Lab Tests Used in the Diagnosis and Management of RA

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Sample</th>
<th>Clinical Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quant. CRP</td>
<td>Blood / Serum</td>
<td>Detect and monitor inflammation</td>
</tr>
<tr>
<td>ESR</td>
<td>Blood / Serum</td>
<td>Detect and monitor inflammation</td>
</tr>
<tr>
<td>RF</td>
<td>Blood / Serum</td>
<td>Autoantibody test, sensitive but nonspecific to RA</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>Blood / Serum</td>
<td>Aid in diagnosis of RA = sensitivity to RF, 95% - 98% specific when RF+ and a CCP+</td>
</tr>
<tr>
<td>RF + Anti-CCP</td>
<td>Blood / Serum</td>
<td>Aid in early diagnosis of RA 99%+ specific when RF+ and a CCP+</td>
</tr>
</tbody>
</table>

Differential Diagnosis

- Systemic lupus erythematosus and other connective tissue disorders
- Polymyalgia rheumatica
- Seronegative spondyloarthropathies
- Crystal deposition arthritis
- Osteoarthritis
- Infectious arthritis
  - Viral arthritis
  - Spirochetal arthritis/Lyme disease
  - Bacterial arthritides/Whipple’s disease
  - Reactive arthritis

Evaluate the Patient with Rheumatoid Arthritis

- Patient’s report of activity
  - Joint pain
  - Morning stiffness
  - Fatigue
  - Function
- Examination
  - Tender/swollen joint counts
  - Mechanical joint problems:
    - Deformity
    - Limited ROM
    - Instability
    - Malalignment
    - Crepitus
  - Extra-articular manifestations
    - Nodules
    - Vasculitis
    - Pulmonary fibrosis
- Laboratory
  - CBC, ESR, qCRP
  - Rheumatoid factor (RF)
  - Anti-CCP
- X-ray
  - Joint space narrowing and/or erosions on x-ray
- Physician and patient overall assessment of disease
- Patient history
  - Comorbid conditions
  - Prior Rx responses
  - Prior Rx side effects

Adapted from ACR RA Guidelines 2002
• PIP swelling
• Swelling is confined to the area of the joint capsule
• Synovial thickening feels like a firm sponge

Joint Swelling

• Prominent ulnar deviation in the right hand
• MCP and PIP swelling in both hands
• Synovitis of left wrist

Bone Erosion

Radiographic Features of Psoriatic Arthritis

Classic pencil-in-cup deformity of DIP joint
Joint space narrowing and erosions; periostitis along shaft of bone in juxta-articular location
X-ray showing asymmetric involvement of sacroiliac joints wherein the right sacroiliac joint is spared and the left sacroiliac joint shows significant narrowing, erosion, and periarticular sclerosis


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Please see Acronym Glossary for term abbreviation definitions.
Radiographic Features of Psoriatic Arthritis

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Clinical Manifestations of Psoriatic Arthritis: Joint Inflammation

- DIP synovitis
- Asymmetric oligoarthritis
- Dactylitis


Indicators of Poor Prognosis in RA

- High titer of RF
- Prolonged elevation of ESR
- High anti-CCP value
- Multiple involved joints
- Extraarticular manifestations of RA
- Reduced functional status
- Early radiographic changes
- Low education/economic status
- Genetics (shared epitopes)

Treat to Target Task Force
(cont)

- Consider structural changes and functional impairment when making clinical decisions
- Choice of measure and target may be influenced by co-morbidities, patient factors and drug-related risks

Treat-to-Target Task Force Algorithm

- Active RA-main target is clinical remission
  - Measure disease activity every 1-3 months
  - Adapt therapy accordingly
  - Once clinical remission attained, measure disease activity every 3-6 months
  - Adapt therapy if remission state is lost
- Alternate target is low disease activity (LDA) and monitoring is the same
**Selected Composite Measures of Disease Activity in RA**

- ACR 20/50/70 used in clinical trials
- DAS 44 requires a 44 joint count, ESR results and a DAS calculator
- DAS 28 requires a 28 joint count, ESR/CRP results and a DAS calculator
- S-DAI requires TJC, SJC, PGA, MDGA and ESR/CRP results added together
- C-DAI requires TJC, SJC, PGA, MDGA results added together

**2010 ACR/EULAR Definitions of Remission in RA Clinical Trials**

- At any point in time patient must satisfy all of the following:
  - TJC ≤ 1
  - SJC ≤ 1
  - CRP ≤ 1 mg/dl
  - PGA ≤ 1 (on a 0-10 scale)
- At any time point, patient must have an S-DAI score of ≤ 3.3

Felson D et al, Ann Rheum Dis 2011, 70; 404-413

**Assessing structural Changes and functional Impairment**

- X-rays
- Musculoskeletal ultrasound with power doppler
- Extremity MRI
- MRI and ultrasound can detect erosions when they are not apparent on x-ray
- The presence of erosions correlates with disability
- There is no data comparing imaging results when switching biologic DMARDs

**Quality Indicators Recommended by the Arthritis Foundation**

- Within 3 months of diagnosis and at appropriate time intervals thereafter:
  - Assess at least 3 joints, functional status, disease activity (presence of synovitis), acute phase reactant (ESR or CRP), and pain (VAS)
  - Obtain baseline radiographs of hands and/or feet (repeat every 3 years)
2012 ACR Recommendations for RA Treatment

- **MTX or leflunomide:** Recommended for most RA patients
- **Hydroxychloroquine or SSZ:** RA pts with low disease activity and absence of poor prognostic factors
- **MTX + Hydroxychloroquine:** RA patients with moderate to severe disease
- **MTX + HCQ + SSZ:** RA patients with moderate to high levels of disease activity and factors that suggest a poor prognosis
- **Anti-TNF + MTX:** Early RA (< 6 mos) with high disease activity and poor prognostic factors
- **Anti-TNF:** RA patients with moderate/high disease activity after 3 mos of MTX (except for infliximab cannot be given as monotherapy)

Singh JA et al. ACR 2012 Recommendations

New Treatment for RA

- **Tofacitinib**
  - First small molecule approved for treating RA
  - Dose is 5mg orally 2 times daily
  - Approved for treating patients with moderately to severely active RA with an inadequate response to methotrexate
  - Works by inhibiting JAK-3 (janus kinase-3) which is responsible for gene transcription of many inflammatory cytokines
  - Increases risk of infection especially of H zoster

2012 ACR Recommendations for RA Treatment

- **Abatacept**:
  - RA patients with moderate to severe disease activity and poor prognostic factors with inadequate response to MTX or other DMARDs
  - Available as monthly IV or weekly subcutaneous injection
  - Approved as first line therapy for RA rather than only for TNF non-responders
- **Rituximab**
  - RA patients with moderate to severe disease activity and poor prognostic factors with inadequate response to anti-TNF therapies
  - Two infusions given 2 weeks apart no more frequently than every 6 months

Singh JA et al. ACR 2012 Recommendations
2012 ACR Recommendations for RA Treatment of High Risk Patients

- Etanercept recommended for patients with hepatitis C
- Biologic agents okay for patients with treated hepatitis B with negative viral load if not Child-Pugh class B or higher
- Biologic therapies okay for patients with solid tumors or non-melanoma skin cancers if more than 5 years ago
- Rituximab for patients with solid malignancy or NMSC less than 5 years ago or any previously treated melanoma

Monitoring for Uncommon Treatment-Specific Side Effects

MTX, leflunomide, or biologics should not be started or resumed in patients with an active bacterial infection, active herpes zoster, active or latent tuberculosis, active life-threatening fungal infections or acute or chronic hepatitis B and acute hepatitis C.

TNF blockers should not be prescribed to RA patients with a history of heart failure NYHA class III-IV or lymphoma and used with caution in patients with MS or other demyelinating disorders.

MTX, leflunomide or minocycline should not be started or resumed for RA in patients planning pregnancy, through pregnancy or while breastfeeding.

Patients should not receive live vaccinations while receiving biologic DMARDs or tofacitinib.

As TNF and JAK-3 inhibitors are thought to decrease natural response to tumor cells, if a patient with RA develops a malignancy, it is recommended to stop the biologic therapy or the JAK-3 inhibitor.

Monitoring for Treatment-Specific Side Effects

- Methotrexate is contra-indicated in the presence of interstitial lung disease. The PI recommends a baseline screening CXR
- Hydroxychloroquine monitoring requires yearly eye exams for peripheral and color vision
- Sulfasalazine (SSZ) monitoring requires CBC and CMP at one month then every 3-6 mos
- Leflunomide/methotrexate monitoring requires CBC, CMP every 4-8 weeks
- Tofacitinib monitoring requires CBC with differential, CMP at baseline, then 4-8 weeks after initiation then every 3 mos and lipids at 4-8 weeks
- Tocilizumab monitoring requires CBC, LFTs every 4-8 weeks and lipids at 4-8 weeks then every 6 mos

Non-Drug Therapy for Rheumatoid Arthritis

- Patient education
  - Chronic, life-long disease
  - Patient must learn about and accept disease
  - A cooperative long-term relationship
  - Materials available from the Arthritis Foundation (www.arthritis.org) and the ACR (www.rheumatology.org)
- Assistive devices to aid performance of activities of daily living
  - Physical or occupational therapists involvement may be necessary where ADL are compromised
- Joint protection
Non-drug therapy (cont)

- Conservation of energy:
  - Balance exercise, activity and rest to achieve the best physical health
- Exercise
  - Decrease fatigue
  - Strengthen muscles and bones
  - Increase flexibility and stamina
  - Improve general sense of well-being
- Exercise options
  - ROM to preserve mobility
  - Isometric exercise for muscle strength
  - If possible, aerobic exercise for conditioning

Drug therapy options for Psoriatic Arthritis/Ankylosing Spondylitis

- The biologic therapies were the first FDA-approved drugs for treating these diseases
- Subsequently, celecoxib (Celebrex) was approved for treating ankylosing spondylitis but most NSAIDs are routinely used in practice
- Non-biologic DMARDs used to treat PsA/AS include sulfasalazine, methotrexate and leflunomide all off-label
- Etanercept (Enbrel), adalimumab (Humira) and infliximab (Remicade) are approved for treating these diseases

Case Study #1

- 61 year-old white female
- 2 month history of pain in fingers, wrists, shoulders, knees
- Swelling in the hands
- 60-120 minutes of AM stiffness
- Unable to play tennis due to hand pain
- Negative family history of RA
- Began 2 weeks after back surgery
- No response to NSAIDs

Case Study #1 (Cont)

- Physical exam normal except joint exam
- Synovitis hands, wrists, right knee with 21 swollen and 2 tender joints
- X-rays show evidence of erosions
- Lab: positive unaltered ANA, Westergren ESR 50, RA 23 (normal < 5), anti-CCP greater than 100, qCRP 10.5 (normal < 5)
- If x-rays showed no evidence of erosions, I would have treated patient with MTX monotherapy but given the presence of erosions I would add biologic therapy to MTX
Case Study #2

- 60 y/o white female
- 6 year history of generalized joint pain
- 30 minutes of AM stiffness
- Diagnosed with RA in 2003 with normal ESR and qCRP, negative RF and anti-CCP, low c4 complement and positive ANA speckled pattern
- No response to low dose MTX or Humira
- Only response is to glucocorticoids

Case Study #2 (Cont)

- Exam normal except for the joint exam
- Synovitis in the elbows, hands, knees, ankles, and feet with 19 swollen and 13 tender joints
- X-rays show no erosions only soft tissue swelling
- Repeat lab 3/09 unchanged except positive anti-cardiolipin antibody panel
- Based on lab results, I stopped the TNF-inhibitor and the patient’s synovitis resolved

Inflammatory Arthritis Summary

- Assess severity of patient’s disease based on history, exam and lab results
  - Current activity
  - Damage
  - Pace
- Begin effective treatment early in most patients with enough power to match the disease
  - Refer early in patients with active inflammatory arthritis
  - Base treatment recommendations on exam, lab and x-ray results
  - Explain to patients that there can be a “disconnect” between symptoms and joint damage
- Alter treatment based on changes in disease activity

Summary: Impact of Early Diagnosis

See www.rheumatology.org and www.arthritis.org for additional rheumatoid arthritis resources
The role of the PA in the care of patients with RA

**Primary Care**
- Evaluate patient with symptoms of inflammatory arthritis (IA)
- If no signs/symptoms of IA, treat with analgesics, exercise and NSAIDs prn
- If signs/symptoms of IA determine severity of disease and refer to rheumatologist if indicated

**Rheumatology Practice**
- Triage patients based on presenting diagnosis
- See patients with signs/symptoms of IA within 2 weeks of referral to begin therapy early on and second visit with MD
- See patients with IA for follow-up visit after consult with rheum

Two take home messages

- If rheumatoid arthritis is diagnosed and treated early in the disease course, the deformity and disability can be prevented in the majority of patients
- Patients with RA must be constantly reassessed for response to therapy and re-evaluated for possible side effects of medications in order to attain maximal benefit from therapy and the PA is well trained to perform these tasks

The Role of Patient Education

- In order to improve patient adherence and compliance with therapy, the benefits and risks of medications must be explained
- The patient also needs to understand the consequences of not treating the disease
- Physician assistants typically play a key role in educating patients
- Recommended sources of patient education include arthritis.org and rheumatology.org
- Patient handouts can be downloaded from these sites and printed out for the patients

Selected References

Kuper S et al, J Rheumatol 2001; 28:1809-1816
Dessein PH et al, J Rheumatol 2006; 33: 201-203.