Rheumatoid Arthritis: Making the diagnosis in primary care

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Disclosure

• Consultant
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  – Purdue Pharmaceuticals
• Speaker bureau
  – Iroko Pharmaceuticals
  – AstraZeneca
  – Depomed Pharmaceuticals

Objectives

• Upon completion of this program, the participant will be able to:
  – Outline the diagnostic criteria for rheumatoid arthritis, its systemic manifestation, and the complication of untreated RA.
  – Identify and discuss laboratory tests that aid in the diagnosis of RA.
Upon completion of this program, the participant will be able to: (cont.)
- Explain the differences between oral disease modifying antirheumatic medications and biologic medications, including medication risks and safety profiles.

1.3 million Americans ages 18 years and older have rheumatoid arthritis. Across most developed countries the incidence is similar, at approximately 0.5% to 1% of adults.

Rheumatoid factors (RF) are antibodies with specificity for antigenic determinates on the Fc portion of human or animal IgG. Currently, the most popular notion that RF arise as antibodies to “altered” autologous IgG.
**Rheumatoid Arthritis**

- A *chronic autoimmune* disease characterized by the *inflammation* of the *synovial joints*.
- Has a symmetrical bilateral effect on joints.
- Results in joint deformity and immobilization.
- Multiple factors increase one's risk.

**Symptoms**

- Morning stiffness lasting more than half an hour.
- Simultaneous symmetrical joint swelling.
- Not relieved by rest.
- Fever.
- Weight loss.

*Source: The Arthritis Society, 2012; Firth, 2011; Oliver, 2010; Day et al., 2010*.
Symptoms (continued)

- Fatigue
- Anemia
- Lymph node enlargement
- Nodules
- Raynaud’s phenomenon

Source: The Arthritis Society, 2012; Firth, 2011; Oliver, 2010; Day et al., 2010

Nodules

Source: Arthritis Foundation, 2012; Day et al., 2010; American College of Rheumatology, 2009

Diagnosis

No single test is specific to rheumatoid arthritis.

- CBC
- Radiographs of involved joints
- CT/MRI scans
- Direct arthroscopy
- Synovial/fluid aspirate
- Synovial membrane biopsy
- Arthrocentesis

Source: National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2012
Inflammatory Markers: ESR and CRP Test

ESR rates for men: 0−15 mm/hr
ESR rates for women: 0−20 mm/hr

- The level of CRP in the blood is normally low.
- Increasing amount suggests inflammation

Source: Day et al., 2010

Antibody Tests
Rheumatoid Factor Test and CCP

Other blood tests check for the presence of antibodies that are not normally present in the human body

Source: National Rheumatoid Arthritis Society, 2012; Day et al., 2010

Synovial/Fluid Aspirate
Synovial Membrane Biopsy
Arthrocentesis

- Arthrocentesis: Synovial fluid is aspirated and analysed for inflammatory components
- Abnormal synovial fluid: Cloudy, milky, or dark yellow containing leukocytes

Source: Day et al., 2010
X-ray

- X-rays are an important diagnostic test for monitoring the disease progression.
- Patients can reveal no changes on an x-ray in the early stages.

Source: Gulani & Myers, 2011; Day et al., 2010

CT/MRI Scans

- Used for better visualization of soft tissue
- MRI is particularly sensitive for the early and subtle features of RA.
- Can detect changes of rheumatoid arthritis prior to an x-ray

Source: Radiopaedia, 2010; Day et al., 2010

Why is early diagnosis and treatment imperative?

- Rheumatoid arthritis progression is the most rapid in the first two years of disease onset.
- 75% of joint damage will occur within the first five years of disease onset.
- Rheumatoid arthritis is as lethal as lymphoma if left untreated!
Diagnostic Criteria for RA
• >4 of the following must be present
  – Morning stiffness >1 hour
  – >3 joints involved
  – Symmetrical swelling; usually in hands, wrists and MTP joints in feet
  – Rotating joint pain

Diagnostic Criteria for RA (continued)
• >4 of the following must be present (cont.)
  – Positive rheumatoid factor (Note: 20% of patients with RA will not test positive)
  – Erosive joint changes on x-ray
  – RA nodules

Complications of Untreated RA
• Pulmonary fibrosis
• Chronic pain
• Disability
• Deformity
• ↓ QOL
• ↑ morbidity and mortality
Labs Eval: Arthritis

- SPEP
- Sed rate
- CBC
- CCP
- RF
- HLA-B27
- CRP
- Hepatic panel
- ANA, ENA, DNA
- Hepatitis panel
- Vitamin D

The Methotrexate Era

- Before the mid 1980s treatment of active RA consisted primarily of gold or penicillamine
- RA is frequently severe and debilitating.
- The adverse effects of DMARDs were problematic.

The Methotrexate Era (continued)

- In 1988 methotrexate was approved for use in RA which was a quantum leap forward.
- Methotrexate remains the cornerstone of therapy of RA today.
The Tumor Necrosis Factor (TNF) Era

- The first biologic for RA, etanercept (Enbrel®), was approved in the U.S. in 1998.
- There are now five TNF inhibitors on the market.
- The TNF inhibitors were a significant addition to our armamentarium which has led to dramatic improvements in patient outcomes.

Treatment: NSAIDs

- Celecoxib (Celebrex®)
- Nabumetone (Relafen®)
- Etodolac (Lodine®)
- Diclofenac and misoprostol (Arthrotec®)
- Piroxicam (Feldene®)
- Diclofenac sodium (Voltaren®)
- Meloxicam (Mobic®)
- Indomethacin (Indocin®)
- Oxaprozin (Daypro®)

Nonsteroidal Antiinflammatories (NSAIDs)

- Most commonly used analgesic for mild to moderate pain
- Have GI, cardiovascular and renal risks
- Annually, 100,000 patients are hospitalized for NSAID-related GI complications alone, direct costs ranging from $1800 to $8500 per patient per hospitalization, 16,500 persons die annually

Source: Fine, 2013 AJMC
Nonsteroidal Antiinflammatories (NSAIDs) (continued)

- FDA latest recommendations: Lowest dose for the shortest period of time
- Newest forms are targeted topical applied to the painful area – patch, gels and liquids - ex. Diclofenac gel (Voltaren® gel), diclofenac patch (Flector® patch)

Treatment: DMARDs

- Methotrexate
- Leflunomide (Arava®)
- Hydroxychloroquine (Plaquenil®)
- Sulfasalazine (Azulfidine®)
- Azathioprine (Imuran®)
- Minocycline (Minocin®)
- Gold sodium thiomalate (Myochrysine®)
- Neoral (Cyclosporine®)

DMARDs
Disease-modifying Antirheumatic Drugs

- Immunosuppressive activity, decreases inflammation of RA, reduces joint destruction, preserves joint function
- Adverse effects: Hepatotoxicity, alopecia, pneumonitis, stomatitis, infertility, aplastic anemia, thrombocytopenia, leukopenia, nephropathy
DMARDs
Disease-modifying Antirheumatic Drugs (continued)

• Special considerations
  – Takes several weeks to months to be effective
  – Teratogenic: Should be taken off therapy several months before conception

Treatment: Biologic Agents

• IL-1 antagonist
  – Anakinra (Kineret®): SC daily

• TNF inhibitor
  – Etanercept (Enbrel®): SC 1–2 times/week
  – Adalimumab (Humira®): SC 2 times a month
  – Infliximab (Remicade®): IV q 6 to 8 weeks
  – Golimumab (Simponi®): SC q month
  – Certolizumab (Cimzia®): SC q month

Treatment: Biologic Agents (continued)

T-cell inhibitor
  – Abatacept (Orencia®): IV q month

B-cell inhibitor
  – Rituximab: IV load, 2 weeks then PRN
Biologic Agents

• Inhibit different inflammatory chemicals (IL2, IL6, TNF) that cause inflammation and damage in rheumatoid arthritis
• Adverse effects: Weight gain, increased blood pressure, depression, mood changes, osteoporosis, delayed wound healing, onset/worsening diabetes mellitus

Biologic Agents (continued)

• Special consideration: Take meds as directed (potential for adrenal suppression), risk for infection

Contraindications of Biologic Agents

• Active lupus
• Tuberculosis
• Active infection
• Hypogammaglobulinemia
• Hepatitis B/C
• CHF III and IV
• Demyelinating disorder
Alternative Medicine

- Olive leaf extract
- Aloe vera
- Green tea
- Omega 3
- Ginger root extract
- Cats claw

Source: American College of Rheumatology, 2012

Omega 3 interferes with blood clotting drugs!

Depression in RA
Pain is subjective and influenced by multiple factors.

Helpless  
Lack of control

Stressful events can increase symptoms of arthritis.
Consider drugs such as paroxetine (Paxil®), amitriptyline (Elavil®) or sertraline (Zoloft®)

Source: Day et al., 2010; Canadian Psychological Association, 2009

Treating Pain in Rheumatoid Arthritis

- NSAIDs and decreasing inflammation is key.
- What if that isn’t enough?  
  - Functionality is goal.
Are opioids appropriate?

Prescribers of opioids should balance the benefits of prescribing opioids to treat pain with the risks of serious adverse outcomes.

Opioid Misuse/Abuse is a Major Public Health Problem

- Improper use of any opioid can result in serious AEs including overdose and death.
- This risk can be greater with ER/LA opioids.

ER opioid dosage units contain more opioid than IR formulations.

Methadone is a potent opioid with a long, highly variable half-life.

In 2011:
- 34.2 million Americans age ≥12 y had used an opioid for nonmedical use some time in their life.

In 2010:
- 425,247 ED visits involved nonmedical use of opioids.
  - Methadone involved in 32% of prescription opioid deaths.
Clinical Interview
Pain and Treatment History

Pain Medications
Past use
Current use
- Query state PDMP where available to confirm patient report
- Contact past providers and obtain prior medical records
- Conduct UDT

Dosage
- For opioids currently prescribed: Opioid, dose, regimen, and duration
  - Important to determine if patient is opioid tolerant

General effectiveness

Nonpharmacologic strategies and effectiveness

Not a Panacea

Rate of Unintentional Drug Overdose Deaths in the United States, 1970-2007

When to Consider a Trial of an Opioid

- Pain is moderate to severe.
- Failed to adequately respond to non-opioid and nondrug interventions
- No alternative therapy is likely to pose as favorable a balance of benefits to harms
- Potential benefits are likely to outweigh harms
- Consider referral to pain or addiction specialist for patients where risks outweigh benefits
- Long-acting opioids: When continuous, around-the-clock opioid analgesic is needed for an extended period of time

Start Low and Go Slow
CDC Guidelines

- Start with lowest effective dosage and increase by the smallest practical amount.
- If total opioid dosage ≥50 MME/day
  - Reassess pain, function, and treatment
  - Increase frequency of follow-up; and
  - Consider offering naloxone.

Start Low and Go Slow
CDC Guidelines (continued)

- Avoid increasing opioid dosages to ≥90 MME/day.
- If escalating dosage requirements
  - Discuss other pain therapies with the patient.
  - Consider working with the patient to taper opioids down or off.
  - Consider consulting a pain specialist.

Initiating and Titrating Opioids

Drug and dose selection is critical. Short-acting vs. long-acting

Check individual drug PI – Fentanyl and hydromorphone ER

Monitor patients closely for respiratory depression

Especially within 24–72 h of initiating therapy and increasing dosage

Individualize dosage by titration based on efficacy, tolerability, and presence of AEs

Check opioid product PI for minimum titration intervals

Supplement w/IR analgesics (opioids and nonopioid) if pain is not controlled during titration

Short-acting Opioids

- Tylenol with codeine: Falling out of favor related to FDA warnings for rapid metabolizers and slow metabolizers
- Doses are limited by the amount of acetaminophen: 4000 mg/day max
- Adverse effect potential: High for nausea and vomiting

Moderate Short-acting Opioids

- Hydrocodone with acetaminophen
- Oxycodone with/without acetaminophen
- Tramadol
- Tapentadol: Dual mode of action as an agonist of the mu-opioid receptor and as a norepinephrine reuptake inhibitor

Strong Short-acting Opioids

- Morphine
- Hydromorphone
- Fentanyl*  
  (*Not for acute pain or opioid naive patient)
When should a patient titrate to a long-acting/extended release opioid?

- When patient is experiencing pain around the clock
- When pain is rated as moderate to severe in intensity
- Rule of thumb: **No more than 4 short-acting opioid doses in a 24 hour period**... If needed then convert to an ER/LA opioid

Exercise

**Being overweight strains joints and leads to further inflammation**

- Walking
- Light jogging
- Water aerobics
- Cycling
- Yoga
- Tai chi stretching

Nutrition

- The most commonly observed vitamin and mineral deficiencies in patients with RA are:
  - Folic acid
  - Vitamin C
  - Vitamin D
  - Vitamin B₁₂
  - Vitamin B₆
  - Vitamin B₁₂
  - Magnesium
  - Vitamin E
  - Zinc
  - Calcium
  - Selenium

Source: Johns Hopkins Arthritis Center, 2012
Braces/Casts/Splints

- Support injured joints and weak muscles
- Improve joint mobility and stability
- Help to alleviate pain, swelling and muscle spasm
- Can prevent further damage and deformity
- Ortho referral may be necessary

Summary

- Refer to rheumatology early and treat aggressively
- Rheumatoid arthritis and inflammatory arthritis shorten the patient’s life expectancy if left untreated
- Many treatment options exist and treatment can be tailored to the patient’s needs.
Questions?

End of Presentation
Thank you for your time and attention.

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