RHEUMATOLOGIC CONSIDERATIONS IN THE GERIATRIC PATIENT

Richard A. Pascucci, DO, FACOI
Vice Dean for Clinical Education
Professor of Medicine
TYPICAL PRESENTATIONS OF RA

1. Insidious polyarthritis
2. Chronic polyarthritis (deforming)
3. Acute migratory polyarthritis
4. Palindromic rheumatism
5. JRA-Still’s Variant
6. Monarticular RA
7. Robust reaction type
8. Rheumatoid nodulosis
9. Elderly Onset

CLINICAL CHARACTERISTICS OF ELDERLY ONSET RA (EORA)

Onset after age 60
Acute onset common
F:M Ratio<3:1
Increased incidence of systemic symptoms
Predilection for large joints

EORA COMPARED TO YORA

<table>
<thead>
<tr>
<th>Increased Incidence</th>
<th>Decreased Incidence</th>
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<tbody>
<tr>
<td>Shoulder &amp; Hip Synovitis</td>
<td>Small Joint disease</td>
</tr>
<tr>
<td>Acute Onset</td>
<td>Extra-articular disease</td>
</tr>
<tr>
<td>PMR-like presentation</td>
<td>Nodules</td>
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<tr>
<td>Elevated ESR</td>
<td>Seropositivity</td>
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REVISED CRITERIA FOR RA (ACR 1987)

- Morning Stiffness
- Swelling of ≥ 3 joints
- Swelling of wrist, MCP, or PIP joints
- Symmetrical joint swelling
- Hand x-ray changes
- Subcutaneous nodules
- Positive Rheumatoid factor

DIFFERENTIAL DIAGNOSIS OF RA

- CTD
- SBE
- Thyroid
- HPO
- Infection
- Osteoarthritis
- Seronegative Spondylitis
- Gout (Tophi)
- PMR (Elderly)
- Rheumatic Fever
- Fibromyalgia

Anti-Cyclic Citrullinated Peptide Ab (Anti-CCP)

- Detected by Elisa technique
- As sensitive as (47-80%) but more specific (97%) than IgM rheumatoid factor
- Marker of erosive disease
- Undifferentiated CTD-may predict RA
- Detected in “Healthy” population years before clinical RA
- Found in 40% “Seronegative RA”
RHEUMATOID ARTHRITIS

• Treat aggressively, EARLY!

• The most significant damage to the joints occurs in the initial 1-2 years of disease.

CURRENT MANAGEMENT OF RA

RITUXIMAB
ABATACEPT

SINGLE AGENT:
SSZ-HCQ-TNF
LEF-GOLD (?)

COMB-TX:
1) MTX & SSZ
2) TRIPLE TX
3) MTX & TNF

ADJUNCTIVE STEROIDS (ORAL OR IA)

MTX

NSAID

Additional TNF Inhibitors

A) Certolizumab Pegol (Cimzia)
   - PEGylated = addition of PEG to reduce antigenicity and immunogenicity
   - Dosage: 400 mg sub q initially, week 2 & week 4
     continued dose dependent upon response

B) Golimumab (Simponi)
   - 50 mg sub q every 4 weeks
Interleukin – 6 Inhibitor (IL-6)

- Tocilizumab (ACTEMRA) –
  - IL-6 Receptor Inhibitor indicated for RA after all infusions (I)
  - TNF Inhibitor has failed
  - Dosage: 4mg/kg IV, increased to 8mg/kg based upon clinical response (1 hour infusion), IV dose every 4 weeks
  - Side Effects: Infections, headache, HTN, LFTs, Anaphylaxis, 1 WBC, or Platelets

XELJANZ (TOFACITINIB)

- Inhibits Janus Kinase (JAK) Enzymes
- Intracellular Enzymes involved in immune cell function via signaling pathway
- Oral Medication
  - Dose: 5mg BID
- Side Effects:
  - Infection/Headache/Gl/Hepatic/Renal

PROGNOSIS OF EORA IN COMPARISON TO YORA

- Shorter duration of the disease
- Improved joint counts
- Lower ESR
- Better physician assessment
A 63-year-old female presents to the office with the complaint of difficulty getting out of a chair. She also has vague symptoms such as fatigue and lack of energy in association with morning stiffness and aching in the proximal portions of her arms and legs. Lab data reveals a mild anemia, normal biochemistry profile, and a westergren sedimentation rate of 75 mm/hr. PE is unremarkable.

**CLINICAL FEATURES OF PMR (SYMPTOMS AND SIGNS)**

<table>
<thead>
<tr>
<th>Pain</th>
<th>Disability</th>
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<tbody>
<tr>
<td>Stiffness</td>
<td>Tenderness</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Limitation of Motion  - areas of involved</td>
</tr>
<tr>
<td>Depression</td>
<td>Arthritis</td>
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<tr>
<td>Carpal Tunnel Syndrome</td>
<td></td>
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**DEFINITION OF PMR**

1. Pain in neck, shoulders, and pelvic girdle for at least one month. Morning stiffness and gelling without muscle atrophy or weakness.
2. Age $\geq$ 50 years old
3. ESR $\geq$ 50 mm/hr
4. Relief of symptoms within 4 days with as low as 10-15 mg Prednisone per day
DIFFERENTIAL DIAGNOSIS OF PMR

RA and other CTD  Osteoarthritis
Viral Myalgias  Fibromyalgia
Polymyositis  Occult CA
Multiple Myeloma  Occult Infection

LAB IN PMR

- Anemia
- ESR (≥ 50 mm/hr)
- RA (-)
- ANA (-)
- Muscle Enzymes – Normal
- EMG – Normal
- Liver Profile

PMR – THERAPY

A) NSAIDS – trial warranted?
- will not prevent vascular complications

B) Corticosteroids - *Drug of choice (low dose)
  If sx free x 6-12 months, may D/C steroids
  50% may relapse
  ? Add MTX (steroid sparing)
  conflicting reports
  Prognosis
  ? Assoc. with ↑ CV mortality

MANAGEMENT OF PMR

- ASA or NSAID’s
- Corticosteroids
  - Dosage
  - Duration
- Biopsy
  - Indications

Education
** N.B. 1 – Sudden Blindness 7 Years After Dx.
N.B. 2 – PMR May Evolve into RA
**GCA – THERAPY**

Corticosteroids 0.7-1.0mg/kg/day
- maintain x one monthly before tapering

* Addition of 81mg ASA
  May prevent occlusive disease

* Add Imuran/CTX/MTX?
  Steroid sparing
RHEUMATIC DISEASES: ASSOCIATED CRYSTALS

Crystal | Disease
---|---
Monosodium urate monohydrate | Gout
Calcium pyrophosphate dihydrate | Pseudogout
Dicalcium phosphate dihydrate | ?
Apatite | Osteoarthritis?
Adrenal corticosteroid esters | Tendon, muscle, and/or synovial calcification
Cholesterol | Iatrogenic postinjection flare
None (chronic effusion)

Patient Demographics of Osteoarthritis

- Affects more than 22 million Americans
- About 80% of patients show x-ray evidence of osteoarthritis by age 55
- Peak incidence reported in patients over age 65
- Women affected approximately twice as often as men

SYMPTOMS OF OSTEOARTHRITIS

- Pain
  - Localized to characteristic joints
  - Aggravated by activity
- Stiffness
  - Generally less than 15 minutes duration
  - With inactivity
- Onset gradual and additive
- Acute and intermittent flares
CLINICAL FEATURES OF OSTEOARTHRITIS

Age: > age 40 (usually)
Morning Stiffness: Usually insignificant
Joint Distribution: DIP, PIP, First CMC, Knee, Hip, First MTP, Spine
Insidious Onset
Rare Systemic Manifestation
Osteophytes and Eburnation

JOINTS USUALLY SPARED IN OSTEOARTHRITIS

MCPs
WRISTS
SHOULDERS
ELBOWS
ANKLES

DIFFERENTIAL DIAGNOSIS OF OSTEOARTHRITIS

RA – ESR, DISTRIBUTION, SYSTEMIC, ETC.
Other DIP Diseases – Psoriatic, Reiter’s
CPPD – Distribution, Flares, Crystals, etc.
Localized Joint Disorders (Early) – Aseptic necrosis, PVS Infections, etc.

Medical Management of OA
Non-Pharmacologic Therapy

• Patient Education – self-help, social support
• Weight loss
• Physical Therapy
  - ROM
  - Strengthening
  - Assistive Devices
• Occupational Therapy
• Aquatic Exercise Therapy
  - Aerobics
Pharmacologic Therapy
• Analgesics – e.g. oral (acetaminophen) or Topical
• NSAID’s
• Opioid Analgesics (e.g. Propoxyphene, codeine)
Experimental Therapies
PHARMACOLOGIC THERAPY FOR PATIENTS WITH OA

**ORAL**
- Acetaminophen
- COX-2 Specific Inhibitor ??
- Nonselective NSAID plus Misoprostol or PPI
- Other Pure Analgesics
- Tramadol
- Opioids
- Intraarticular
  - Steroids
  - Hyaluronan
- Topical
  - Capsaicin
  - Methylsalicylate
*Choice of Agent(s) should be individualized


**Glucosamine Sulfate-Chondroitin Sulfate**
- Repair and Maintenance of Cartilage
- Several short-term controlled human studies show modest decrease OA symptoms
- May have Remittive Effect

**Hyaluronic Acid Treatment**
- *Viscosupplementation*
  - Injected into knee joint for 3-5 consecutive weeks
  - Equally as effective as Acetaminophen (pain relief) or Naprosyn
  - No proof of altered joint Biology
  - FDA Approved – side effects include local irritation or severe allergy (rare)

**Future Directions in OA Therapy**
- MMP inhibitors
- NO inhibitors
- COX-2 specific inhibitors
- Disease-modifying interventions

LATE-ONSET SLE

Occurrence after age 50
F>M
Frequent Misdiagnosis
Conservative Therapy

LATE-ONSET SLE CLINICAL MANIFESTATIONS

Arthritis
Rash
Constitutional Sx.
Pleuritis/Pericarditis
Nephritis
Hematologic
### LATE-ONSET SLE

#### LESS COMMON CLINICAL FEATURES

- Lymphadenopathy
- Raynaud’s Phenomenon
- Neuropsychiatric Disease
- Alopecia

### DRUG – INDUCED SLE

1. Criteria
2. Female:Male Ratio
3. Black vs. White
4. System Speared
5. Serum Antibody
6. Clinical Symtoms
7. Predisposition –
   - (a) HLA – type
   - (b) Slow Acetylator

### Lupus-like Syndrome: Drugs Implicated in Induction

- **Anticonvulsants**
  - Ethosuximide
  - Mephonytoin
  - Phenytoin
  - Primidone
  - Trimethadione

- **Antimicrobial agents**
  - Grisoeifulvin
  - Isoniazid
  - Nitrofurantoin
  - Penicillin
  - Streptomycin
  - Sulfonamides
  - Tetracycline

- **Anthypertensives**
  - Hydralazine
  - Methyllopa
  - Reserpine
Lupus-like Syndrome: Drugs Implicated in Induction (continued)

Antithyroid agents
- Methylthiouracil
- Propylthiouracil

Cardiovascular agents
- β-Adrenergic blocking agents
- Procainamide
- Quinidine

Psychotropic agents
- Chlorpromazine
- Lithium carbonate

Miscellaneous
- Allopurinol
- Aminoglutethimide
- D-Penicillamine
- Gold Salts
- Methysergide
- Oral contraceptive
- Phenylbutazone
- Biologic Agents

Prevention | Treatment
--- | ---
Alendronate | Yes | Yes
Risedronate | Yes | Yes
Calcitonin | No | Yes
Conjugated Estrogens | Yes | No
Raloxifene | Yes | Yes
PTH | No | Yes

Treatment of Postmenopausal Osteoporosis

FDA-Approved Indications
TEIPARATIDE TX. FOR OSTEOPOROSIS

- Approved November 2002
- Anabolic Agent

Indications: (1) Post-Menopausal ♀ @ High Risk for fx
- Previous fx
- Signif. Low Bone mass
- Intolerant or unresponsive to other Tx.
(2) ♂ - Primary or hypogonadal osteoporosis

CI | Paget’s | ESRD
---|---------|------
Pregnancy | METS |
Osteomalacia | Stone Disease |

TERIPARATIDE TX. FOR OSTEOPOROSIS CONT.

Risks: ↑ Osteosarcoma in Rats
(Use only for 2 years)
Side effects: Dizziness & Leg Cramps

Baseline lab: CA++ Alk. Phos.
Po4 = 25-OH Vit D. Creatinine
Dose: 20 ug Sub = Q daily
Cost: AWP = $7592/year

COMBINATION THERAPY

A) "The Effects of Parathyroid Hormone and Alendronate alone or in combination in postmenopausal osteoporosis"
Black DM, Greenspan SC, Ensrud KE, ET AL.
NEJM - September 25, 2003
Conclusion: No Evidence of synergistic effect

B) Raloxifene + PTH
Combination Better Than PTH alone.
Deal, C.- Presented at ACR (October 2004)

DENOSUMAB

- Anti-Resorptive agent
- Inhibits Rankl

Trial Compared Denosumab to Alendronate (open case)
(412 pm O with low bone mass)
Denosumab
60 mg sub Q every 6 months
Results (24 months)

- Denosumab
  - BMD HIP: ↑ 5%
  - BMD L. SPINE: ↑ 7%
  - BMD Radius: ↑ 1.75%

- Alendronate
  - BMD HIP: ↑ 3.5%
  - BMD L. SPINE: ↑ 6%
  - BMD Radius: ↑ 0.5%
RANKL –

Receptor Activator of nuclear factor KAPPA B Ligand

- Mediates resorptive phase of bone remodeling
- Blocking the binding of RANK to its ligand inhibits the Osteoclast
Bisphosphonates and Fractures of the Subtrochanteric or Diaphyseal Femur

DM Black, MP Kelly, KH Genant, L. Paiermo et al.
NEJM 362:19, 1771–1777; May 13, 2010

*Secondary Analysis of Large, Randomized Bisphosphate Trials:
1) FIT (Fracture Intervention Trial)
2) FLEX (FIT Long-Term Extension)
3) HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid once yearly) Pivotal Fracture Trial (FPT)

Results: Review of 284 records for hip or femur fractures among 14,195 in these trials.

12 Fractures in 10 patients occurred in subtrochanteric or diaphyseal femur (2.3 per 10,000 patients years).

Bisphosphonates and Fractures of the Subtrochanteric or Diaphyseal Femur (Con’t)

*Relative Hazard: 1.03 in FIT
1.33 in FLEX
1.50 in HORIZON-FPT

Conclusions: 1) Occurrence of atypical fracture was rare, even among patients TX for 10 years
2) No significant increase in risk (but study underpowered for definitive conclusions)

* Not Significant

Editorial

Evolving data about Subtrochanteric Fractures and Bisphosphonates
Elizabeth Shae, MD
Columbia Univ., New York
NEJM 362:19, 1825–1827; May 13, 2010

- Atypical fractures usually proximal 1/3 of femur, usually transverse & may have shallow oblique configuration. May be bilateral & association with medial spike, cortical thinning & prodromal thigh pain
- Concerns clinicians but: Nearly 24% of all hip fractures (1.6 million worldwide in 2000) were subtrochanteric
- Not all associated with Bisphosphonates
- Such atypical FX have NOT increased since bisphosphonates

Editorial (Con’t)

What are the implications of the Black et al Study for Clinical Practice?

1) Subtrochanteric FX are extremely rare
2) Many more devastating hip fractures are prevented by Bisphosphonates than potentially caused by them
3) Detailed recommendations beyond scope of this editorial – consider Drug Holiday (low bone turnover markers)
4) Use of alendronate for 10 years compared to 5 years was associated with significantly fewer vertebral and non-vertebral FK in PFTs with BMD – 2.5 or below

E. Shane, MD
“The Effects of Strontium Ranelate on the Risk of Vertebral fracture in women with post menopausal osteoporosis”

NEJM 350:5, 459-468, Jan-29, 2004

STRONTIUM RANELATE

“Re-Launched” as a new compound

Mode of Action
- Stimulates Bone Formation
- Decreases Bone Resorption
- May Suppress PTH
- No Mineralization Defects

Dosage: 2 Grams/Day

VERTEBROPLASTY

Utilizes cement injection into bone for stabilization of compression fracture(s)

Patient Selection
- (1) Severe Back pain < 12 months - (Refractory to analgesics)
- (2) Vertebral body compression fracture(s) - (Pain elicited with palpation at specific level(s))
- (3) MRI/Bone scan-no other explanation
  *Osteoporotic or pathologic Fx treated

Summary
- Recognize that Osteoporosis is a preventable and often a clinically silent disease
- Understand the NOF guidelines and incorporate them into your daily practice
- Utilize the FRAX tool to maximize the management of your patients
- Be familiar with the preventive and therapeutic options available
Osteoporosis Therapy Options Postmenopausal Women

During Hot Flashes
ET/EPT

Past Vasomotor Symptoms
Bisphosphonates
Raloxifene
Teriparatide
Calcitonin

After Fracture

Physiologic\nStimulus
COX-1\nConstitutive

Inflammatory\nStimulus
COX-2\nInducible

* Platelets
* Endothelium
* Stomach
* Kidney

TXA2, PGI2, PGE2

"HOUSEKEEPING"

NONSTERoidal ANti-INFLAMMATORY\nDRUGS (NSAIDs)

- Largest class of pharmaceutical agents used worldwide
- Cornerstone agents in the pharmacologic therapy of arthritis
- Effective in relieving pain, inflammation, and stiffness in arthritis patients
- Enhance function and improve quality of life in arthritis patients
- Good safety profile when prescribed and monitored appropriately

UTILIZATION OF NSAIDs

2000 - 111,400,000 Rx for NSAIDs in US
- $5 Billion Cost
- $2 Billion OTC NSAIDs
- 34% age ≥ 65 use on daily basis

Today 17,000,000 Americans utilize on daily basis
- $10 Billion Market Worldwide
- Marketed directly to consumers
USE OF NSAIDs

- Osteoarthritis
- Rheumatoid Arthritis
- Other arthritic conditions
- Pain syndromes
  - musculoskeletal pain syndrome
  - soft tissue pain syndrome

MECHANISM OF ACTION OF TRADITIONAL NSAIDs AND COXIBs

COX-1
- "Constitutive"
- Non-specific NSAIDs
- COX-2
- "Innocible"

- Arachidonic acid
- Prostaglandins
- Thromboxane
- Prostaglandins
- Protection of Gastric Mucosa
- Platelet Function and Hemostasis
- Mediate Pain, Inflammation, and Fever

TOXIC EFFECTS OF NSAIDs

- GI disorders (dyspepsia, PUD, occult bleed)
- CNS
- Tinnitus
- Rash
- Hypersensitivity Reactions (ASA Allergy)
- Hepatotoxicity
- Nephrotoxicity (edema, K+, ARF, papillary necrosis, interstitial nephritis)

Protective Effect of Chronic NSAID Use on Cognitive Decline in Older Persons

- Interview Study of 7871 Patients (personal-3 and Telephone-4)
- Utilize SPMSQ (Short, Portable Mental Status Questionnaire)
- Chronic NSAID Usage (3 years at 2 Interviews)
- Role of Amyloid (?) in Alzheimer’s
SUMMARY: BENEFITS OF COX-2 SPECIFIC INHIBITION

- COX-2 Specificity
  - Inflammation and pain reduced, similar to non-selective NSAIDs
- COX-1 sparing
  - GI toxicity reduced, in contrast to non-selective NSAIDs
- Lack of effect on platelets

Hypothesis

- Inhibition of vascular PGI2 (Prostacyclin) synthesis
- Lack of Effect on Platelet Thromboxane Synthesis
- Imbalance
- Prothrombotic State
- Increased Thromboembolic CV Events

COXIBs/NSAIDs
(Traditional or Non-Selective)
Questions to be Answered

CV

- Role of COXibs and CV Thrombotic Events
- Effect of NSAID + ASA on MI Prevention
- Do Non-Selective NSAIDs cause MI? (Traditional)

HISTORY OF CV EVENTS WITH COXIBs

- VIGOR Trial - Bombardier, et al. 2009: Disappearance of data after 6 weeks of therapy
- CLASS Trial - Silversmith, et al. 2000: No statistical significance
- APPROVe Trial - (Adenoma Prevention on Vioxx) Recruitment began 2005 (100,000 Patients)
  Disappearance after 18 months (Twice as frequent thrombotic events)
  1600 pts. Suspension of Authorization for parecoxib in April 2005
**COX-2 PROVEN TO BE DOMINANT SOURCE OF PGI₂ (PROSTACYCLIN)**

- Vasodilation
- Inhibits Platelet Aggregation
- Prevents Proliferation of vascular smooth muscle cells (In Vitro)

Fitzgerald, GA: NEJM 351:17 (October 17, 2004)

**COXIBs/NSAIDs & HEART DISEASE**

A) Blood Pressure
B) Fluid Retention
C) Oxidative Modification of Biologic Lipids (possible) leading to atherosclerosis
D) Exacerbation of CHF (esp. with , Renal Fx.)


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**Cox-2 Cardiovascular Effect**

**HYPOTHESIS**

Inhibition of vascular PGI (Prostacyclin) synthesis
And
Lack of Effect on Platelet Thromboxane Synthesis
↓ Imbalance
↓ Prothrombotic State
↓ Increased Thromboembolic CV Events

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**Is CV Disease a COX-2 Class Effect?**

* Events more likely with higher dosage and longer duration of therapy.
* Inconclusive evidence of class effect.

**Recommendation:** Utilize a Risk/Benefit analysis of each patient
N.B. Patient with Inflammatory disease at higher risk for MI

Inhibition Of Clinical Benefits Of Aspirin On First Myocardial Infarction By NSAIDs


Findings: ASA 325 mg q other day, rate of 1st MI by 44% before NSAID use for 1-39 Days/yr = no change
- NSAID use (e.g. Ibuprofen) > 40 days/yr = ↑ risk MI

Conclusions: Possible that differences in inhibition of ASA's effect on platelets may lead to differences in clinical outcome (not yet proven)

* Diclofenac & Refecareb had no effect

Recommendation: Take ASA at least 2 Hours prior to the NSAID

LONG TERM USE OF NSAIDs And The Risk of Myocardial Infarction In The General Population


- Nested case-control analysis of 4975 cases of acute MI and 20,000 controls (86-84 Y.O.)
- NSAID use (Ibuprofen, Diclofenac, Naproxen) for < 1 year did not ↑ risk for MI
- NSAID use for > 1 year ↑ risk for nonfatal MI
- Diclofenac reached statistical significance for small risk while naproxen may have reduced risk. Ibuprofen revealed an unclear risk (no statistical signal)
- The use of ASA counteracted the risk for MI

RISK OF MI WITH PROLONGED USE OF TRADITIONAL NSAIDs

- Numerous trials with variable results
- ASA appears to obviate risk with NSAIDs
- Interaction between ibuprofen (and others) and ASA not substantiated
- NSAIDs alone do not appear to offer Cardioprotection

Summary & Recommendations:
1) Take ASA 2 hours prior to NSAID
2) Must take ASA + NSAID if at risk for CAD
Recommendations (Considerations) for the use of NSAID/Cox-2 in 2006

- Careful consideration to the patient needs (indication) for an NSAID or COX-2 (Avoid with CAD)
- Prescribe NSAID/COX-2 to those with the lowest cardiovascular (CV) and/or GI risk if possible
- Involve patient in discussion for Decision-Making
- Consider alternative therapies (Analgesics, Injections, Topical) if the risk is determined to be too great.
- Utilize the lowest effective dose for the shortest period of time.
- During therapy: Monitor patients for signs of developing toxicities

Andrew K. Brown in International Journal of Advances in Rheum. Vol 3 No. 4, 2006

MONITORING NSAID THERAPY

Initially: CBC UA K+ SGOT Creatinine

\{ Q 1 3 Months \}

Stable: Same Lab Q 3 12 months

From: Guidelines for Reviewers of Rheumatic Disease Care ACR (CORC)