Pathophysiology of Rheumatoid Arthritis & Osteoarthritis

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November 15, 2007
A Superficial and Informal Overview of a Patient with ‘Aches & Pains’

- Musculoskeletal pain
- Rheumatoid arthritis
- Osteoarthritis
Away from Musculoskeletal System
“Referred” Visceral Neurological

Within Joint “Arthritis”
Subchondral bone Cartilage Synovial fluid Synovium

Away From Joint “Non-articular” Muscle Bone

Around Joint “Peri-articular” Muscle Tendon Tenosynovium Enthesis Bursa Ligament
Rheumatoid Arthritis

- Chronic
- Inflammatory
- Polyarticular
- Symmetrical
- Involves PIP/MCP/Wrist/MTP
- Synovial Proliferation
- Erosive
Inflammatory Arthritis

- **History**
  - rapid onset
  - waxing/waning course
  - red/hot joint
  - inflammatory pain: use, rest, night
  - profound, prolonged morning stiffness
  - systemic findings

- **Physical examination**
  - red/hot joint (but inflammatory arthritis uncommonly has red/hot joints)
  - SYNOVITIS
RA - Inflammatory Arthritis

- Onset in days, weeks, months; not “years”
- Waxing/waning course
- Inflammatory pain
  - pain with use
  - pain at rest
  - night pain
- Morning stiffness: profound/prolonged

- Systemic inflammation
  - symptoms
  - signs
  - labs
- Physical exam
  - inflammatory joint fluid
  - “synovitis”
Stages of RA

Early

Intermediate

Late

RA Progression

Graph: Adapted from Kirwan JR. J Rheumatol. 2001;28:881-886.
The Synovial Membrane

Normal synovial membrane, photomicrograph
Pathophysiology of RA

Synovitis, villous, gross (left) and photomicrograph (right)
Pathogenesis of RA

Immunobiology of Rheumatoid Arthritis

- APC
- CD4+ T cell
- MHC
- Peptide
- TCR

- IL-1
- IFNγ
- TNFα
- IL-2
- IL-6
- IL-4
- TGFβ
- TNFβ

- B Cells
- Synoviocytes
- Adhesion
Cytokines

- Secreted polypeptides
- Control
  - cellular function
  - differentiation
  - intercellular communication
- Important mediators of immune & inflammatory responses
The Summary of RA Pathology

Choy EHS, Panayi GS.
NEJM 2001;344:907-916
Cytokine Disequilibrium in RA

Pro-inflammatory

- TNF-α
- IL-1
- IL-6

Anti-inflammatory

- sTNFR
- IL-1ra
- sIL-1R
- IL-4
- IL-11
Synthesis and Actions of TNF$\alpha$
RHEUMATOID ARTHRITIS: Role of TNF-α

- TNF-α is a potent cytokine that stimulates a variety of pro-inflammatory cells
- TNF-α is produced mainly by monocytes & macrophages
- TNF-α is a major contributor to the inflammatory and destructive changes that occur in RA
- Blockade of TNF-α results in reduction in the levels of other pro-inflammatory cytokines, such as IL-1, IL-6, and IL-8

RA: Extra-articular Manifestations

- Systemic sx/signs
- Anemia of chronic disease
- Nodules
- Vasculitis
  - hypersensitivity
  - PAN-like
- Neuropathy

- Ophthalmologic
- Pulmonary
  - fibrosis
  - nodules
  - effusions
- Felty’s syndrome
- Sjogren’s syndrome
## Rheumatoid Factor

<table>
<thead>
<tr>
<th></th>
<th>% of patients with +RF</th>
</tr>
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<tbody>
<tr>
<td><strong>Normal</strong></td>
<td></td>
</tr>
<tr>
<td>Young</td>
<td>0.7-2</td>
</tr>
<tr>
<td>Old</td>
<td>10-24</td>
</tr>
<tr>
<td><strong>Non-rheumatic disease</strong></td>
<td>0-50</td>
</tr>
<tr>
<td><strong>Rheumatic disease</strong></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>85</td>
</tr>
<tr>
<td>Other</td>
<td>0-74</td>
</tr>
</tbody>
</table>
Rheumatoid Factor

• **Positive RF**
  – Does NOT diagnose RA by itself
  – If “high titer”
    • increased risk of RA
    • more severe disease
  – Little change in titer with course

• **Negative RF**
  – Does NOT exclude RA
Goals in Treating RA

• Treat current symptoms: pain, stiffness, swelling, decreased range of motion, function

• Prevent structural damage

• Improve long term outcome: disability, death
Treatment of RA

• Education
• PT/OT, Vocational rehabilitation
• NSAIDs
• Disease Modifying Anti-Rheumatic Drugs (DMARD)
• Biologic therapy

In some patients
• Intra-articular, I/M or oral Steroids
• Surgery for pain/function improvement, deformity
All patients with RA should be treated with DMARDs as soon as diagnosis is made

- Gold, d-Penicillamine
- Hydroxychloroquine, Minocycline, Sulfasalazine
- Methotrexate, Azathioprine, Leflunomide
- Cyclosporine, Cyclophosphomide
- TNF inhibition: etanercept/infliximab/adalimumab
- IL-1 receptor antagonist: anakinra
- Anti-CD 20 monoclonal antibody: Rituximab
- Co-stimulation blocking agents: Abatacept
Toxicities of DMARDs

- **Hydroxychloroquine** (*Plaquenil*)
  - retinal
- **Sulfasalazine** (*Azulfidine*)
  - photosensitivity
  - GI (dyspepsia)
  - leukopenia
- **Gold** (*Myochrysine, Solganal*)
  - rash/oral ulcers
  - thrombocytopenia
  - proteinuria
- **Methotrexate**
  - GI/rashes
  - hematologic
  - lung
  - liver (cirrhosis)
- **Leflunomide** (*Arava*)
  - GI/diarrhea
  - hematologic/liver/skin
- **Azathioprine** (*Imuran*)
  - leukopenia/infection
  - ? lymphoma
Prednisone in RA

Prednisone may be the most effective medical therapy for RA.

Prednisone may be the most toxic medical therapy for RA.

When is prednisone indicated in RA?

- “Bridging Therapy”: providing some control while DMARDs are beginning to work.
- Extra-articular disease.
- RA in the elderly: PMR-like; low-dose prednisone vs. high-dose NSAIDs.
Inhibition of Cytokines

Soluble Receptor Neutralization of TNFα

Macrophage or activated T-cell

Etanercept (Enbrel)

TNF receptor

Target cell
Soluble receptor constructs bind & neutralize soluble TNF-\(\alpha\) & \(\beta\), but not membrane-bound TNF-\(\alpha\)
Antibody Neutralization of TNFα

Macrophage or activated T-cell

Infliximab (Remicade)  Adalimumab (Humira)

TNF receptor

Target cell
Monoclonal Antibodies Bind and Neutralize Both Soluble and Membrane-bound TNF-α
B Cells May Act at Multiple Sites in the Autoimmune/Inflammatory Process

- B cells play a role in the pathogenesis of RA
  - Antigen presentation & T-cell activation
  - Production of pro-inflammatory cytokines
  - Production of RF & other autoantibodies
Rituximab: anti CD20 mab

- Genetically engineered chimeric murine/human monoclonal antibody to CD20
- IgG1 kappa immunoglobulin, murine light & heavy chain variable sequence & human constant region sequence
- Selectively binds CD20 molecule with high affinity ($K_d$ 8.0 nM)
- Half life: 18-21 days

Rituximab
Mechanisms of Action

ADCC = antibody-dependent cell mediated cytotoxicity.
CDC = complement-dependent cytotoxicity.

Activation of Naïve T cell Requires two signals

1. Peptide/MHC complex plus CD4
2. Co-stimulatory B7.1 (CD80) or B7.2 (CD86) on APC & CD28 on T cell
T cell activation through CD28 leads to increased expression of CTLA-4 (cytotoxic T lymphocyte associated antigen 4) on T cell surface, an alternative receptor for B7

CTLA-4 has higher affinity for B7
CTLA-4 down-regulates T cell activation
Abatacept Mechanism of Action

Antigen activation

Inhibition

Costimulation

Unresponsiveness
## Biologic DMARDs

<table>
<thead>
<tr>
<th>Class</th>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Adalimumab</th>
<th>Anakinra</th>
<th>Rituximab</th>
<th>Abatacept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombin construct</td>
<td>sTNFR mAb</td>
<td>TNF-α mAb</td>
<td>TNF-α mAb</td>
<td>IL-1Ra</td>
<td>CD-20 mAb</td>
<td>Chimeric</td>
</tr>
<tr>
<td>Human</td>
<td>Human</td>
<td>Human</td>
<td>Human</td>
<td>Human</td>
<td>Chimeric</td>
<td>Human</td>
</tr>
<tr>
<td>Half-life</td>
<td>4.3 d</td>
<td>8-10 d</td>
<td>10-20 d</td>
<td>4-6 hrs</td>
<td>15-21 d</td>
<td>13 d</td>
</tr>
<tr>
<td>Primary binding target</td>
<td>TNF-α</td>
<td>TNF-α</td>
<td>TNF-α</td>
<td>Type I IL-1R</td>
<td>CD-20 B Cell</td>
<td>CD-80 CD-86</td>
</tr>
<tr>
<td>Admin</td>
<td>25 mg sc 2x/wk</td>
<td>3-10 mg/kg Q4-8 wk iv + MTX</td>
<td>40 mg sc eow</td>
<td>100 mg/d sc</td>
<td>1000 mg iv d1 &amp; 15</td>
<td>10 mg/kg Q4 wk</td>
</tr>
</tbody>
</table>
New Biologics to Treat RA on the Horizon

- Certolizumab (Cimzia): Humanized PEG-ylated monoclonal antibody against TNF (only FAB, no Fc)
- Tocilizumab (Actimra): humanized monoclonal antibody to IL-6 receptor
- Atacicept and Belimumab: new B cell directed agents
Rheumatoid Arthritis

- Chronic
- Inflammatory
- Polyarticular
- Symmetrical
- Arthritis: PIP/MCP/Wrist/MTP
- Synovial Proliferation, Erosive
- Needs immediate treatment with DMARDs
- Newer anti-cytokine treatments are very effective
Non-inflammatory Arthritis

• History
  – slow steady progression
  – no “believable” red/hot joints
  – mechanical pain: ↑ use, ↓ rest/night
  – no profound/prolonged morning stiffness
  – no systemic findings

• Physical exam
  – swelling:
    • effusion/osteophytes/ligaments
  – crepitus/grating
  – local joint line tenderness
Osteoarthritis – Risk Factors

- Age
- Gender – women > men
- Genetic predisposition
- Trauma
- Obesity
- Quadriceps muscle weakness
- Heavy physical activity
Osteoarthritis

• **Primary/nodal OA:**
  – DIP: Heberden’s nodes
  – PIP: Bouchard’s nodes
  – 1\textsuperscript{st} CMC

• **Secondary OA**
  – knee/hip
  – trauma

• **Spinal OA/degenerative disk disease**
Pathophysiology

- Primarily a disease of cartilage
- Cartilage made up of water, proteoglycans and collagen
- Mechanical stress across joints may initiate process followed by cartilage degradation
- Ultimate loss of joint architecture
Osteoarthritis = Joint failure
Osteoarthritis

• Not just “degeneration”
• Osteoarthritis is an “active” process
  – Ineffective repair
  – Chondrocyte dysfunction
  – Protease activation (MMP, Collagenase)
  – Cytokine/growth factor elaboration
• “Active” processes can be treated (?)
Osteoarthritis

• Pathogenesis:
  – genetic factors
  – altered biomechanical forces
    (abnormal pressure to normal cartilage or normal pressure to abnormal cartilage)
  – pre-existing diseases of the hip/knee

• Management designed to reduce symptoms and improve function
Radiographic Changes in OA

- Joint space narrowing
- Subchondral sclerosis
- Subchondral cysts
- Osteophytes
Osteoarthritis of the Knee
ACR Classification Criteria

• Knee pain and radiographic osteophyte and at least 1 of the following:
  – age > 50 years
  – morning stiffness ≤ 30 minutes
  – crepitus on motion
Early Stage of Osteoarthritis:
- Degeneration of Cartilage
- Cartilage Particles

Late Stage of Osteoarthritis:
- Loss of Cartilage
- Bony Hypertrophy
Clinical Findings in Osteoarthritis

• Arthritis: pain with use, limited/painful ROM

• Non-inflammatory arthritis:
  – Slowly progressive
  – Mechanical pain: ↑ use, ↓ rest/night
  – Little morning stiffness
  – “Gelling”
  – Crepitus/grating
  – Joint enlargement: bone, effusion, ligaments
  – Joint line tenderness
Goals in Treating Osteoarthritis

• Treat pain
• Protect joint
• Stabilize/improve function
• ? Prevent further deterioration
Treatment

- Pharmacologic vs Non-pharmacologic
- Two Primary Goals
  - Treat pain
  - Improve function
Medical Management of OA
ACR Guidelines

• Original Publication in 1995
• Ad hoc subcommittee established 1998
• ‘Evidence based medicine’ approach
• New guidelines published Sept 2000

ACR Guidelines 2000
Non-pharmacological Therapy

• Patient Education, Self management programs, social support
• Weight loss if overweight
• PT: aerobic strengthening exercises, ROM
• Assisted device, footwear, insole, bracing
• OT: joint protection, energy conservation

Non-pharmacologic Treatment

• Exercise – strengthening, flexibility, aerobic
• Weight loss
• Orthotics/assistive devices
• Alternative remedies
  – Glucosamine/chondroitin
  – Vitamin C/D (low intake- risk of progression)
  – Herbals
Exercise therapy - goals

• Decreases pain
• Improves function
  – Posture
  – Gait stability
  – May reduce falls
Exercise therapy

- Exercise program should be tailored to individual patient
- Flexibility, strength and endurance
- Goal oriented program
- Caution for musculoskeletal injury
- Contraindications to exercise – heart disease, poorly controlled hypertension
ACR Guidelines 2000
Pharmacological Therapy: 1

• Oral
  – Acetaminophen
  – COX-2 specific inhibitor
  – Non-selective NSAID plus misoprostol/PPI
  – Non-acetylated salicylate
  – Other pure analgesics:
    • Tramadol
    • Opioids
NSAIDs Overview

• Consumption: 30 million in US
• Sales: $6 billion/year worldwide
• Uses: the aches and pains of life
• Problems: GI, renal, platelets
• Dyspepsia: common
• Estimated deaths: > 10,000/year in US, due to ulcers and bleeding
Described an extract of seminal fluid which caused uterine contraction - “Prostaglandin”

Nobel Prize in 1970 for describing the release of nor-adrenaline from sympathetic nerves

Bengte Samuelson

Sune Bergstrom

John Vane

Nobel Prize in 1982 for “their discoveries concerning prostaglandins”
Cell Membrane Phospholipids

Phospholipase A₂

Arachidonic acid

Cyclooxygenase

PGH₂

PGD₂, PGE₂, PGF₂α, PGI₂, TXA₂
Number of Deaths $2^0$ NSAID Damage Compared with Other Causes: 1997*

*National Center for Health Statistics, 1998

Causes of Death

Mechanism of Action of COX-2

Selective NSAIDs

Normal Physiologic Stimulus

- GI protection
- Platelet Aggregation
- Regulation of blood flow
- Kidney function
- Sensory processing

Inflamatory Stimulus

- Inflammation
- Pain
- Fever

ARACHIDONIC ACID

Constitutive

COX-1

Inducible

COX-2

Prostaglandins

Selective COX-2 Inhibitors
COX-2 Specific Inhibitors: Chemical Structures

Celecoxib

Rofecoxib

Valdecoxb
Merck Announces Voluntary Worldwide Withdrawal of VIOXX®

WHITEHOUSE STATION, N.J., Sept. 30, 2004—Merck & Co., Inc. today announced a voluntary worldwide withdrawal of VIOXX® (rofecoxib), its arthritis and acute pain medication. The company’s decision, which is effective immediately, is based on new, three-year data from a prospective, randomized, placebo-controlled clinical trial, the APPROVe (Adenomatous Polyp Prevention on VIOXX) trial.

Merck & Co. CEO Raymond V. Gilmartin announcing the withdrawal of Vioxx
COX-2 Inhibition & MI

Hypothesis

Arachidonic acid

COX-1

TXA₂

Platelet Aggregation

COX-2

PGI₂

Vasodilatation
ACR Guidelines 2000
Pharmacological Therapy: 2

• Intra-articular:
  – Glucocorticoids
  – Hyaluronic acid

• Topical
  – Capsaicin
  – Methylsalicylate
Viscosupplementation

• Synvisc® and Hyalgan®
• Synthetic hyaluronic acid
Viscosupplementation

- Improve lubrication, nutrition, and function of articular cartilage
- Efficacy is variable
- Patients with early OA and moderate symptoms benefit most (not indicated with ‘bone-on-bone’’
“Alternative” Therapies

- Glucosamine/chondroitin
- SAMe
- Magnets
- Anti-inflammation diets
- DMSO
Alternative Medications

CAUTIONS

• NOT FDA regulated
• Unclear effective dosage
• Minimal data on toxicity – especially with long term use
• Not currently recommended until further studies are available
Glucosamine/Chondroitin

- Widely used in Europe for > 10 years
- Very few side effects (diabetics should watch their blood sugars)
- Not FDA approved, so no strict quality control
Glucosamine

- Found in normal cartilage where they are believed to play a role in formation & repair
- Sulfate, hydrochloride, N-acetyl, chlorhydrate
- ‘Disease Modifying’ or ‘Anti-inflammatory’
- Source for supplements: shells of crabs, lobsters and shrimp
Chondroitin

- Limited studies compared to Glucosamine
- Derived from cattle, only 10% absorbed orally
- ? Anti-inflammatory, ? Disease Modifying
- May improve pain & function when compared with placebo
Glucosamine/chondroitin

• The sulfate form (rather than chloride) is recommended

• Optimal dose is unknown – in studies, patients took 1500mg/day glucosamine and 1200mg/day of chondroitin

• If no improvement after 3 months, save your money
SAMe

• S-adenosylmethionine
• Molecule involved in a number of metabolic processes
• Anti-depressant effect in patients with RA
• Anti-inflammatory effects in animal studies
• Analgesic effects in patients with mild to moderate OA – as effective as NSAIDs in some studies
SAMe

- No serious side effects
- Mechanism of action unknown (anti-depressant activity)
- Dose used in studies: 200 – 400 mg 3 times daily
- May take a month to have an effect
- Renewed interest of late (possibly in the wake of glucosamine...
Others

• Avocado and soybean unsaponifiables – action unknown
• Acupuncture - ??
• Surgery - joint replacement is indicated for severe pain, not for functional improvement
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enhanced by strategically-placed magnets.
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#39700GD Gold Deluxe (middle) 3 oz
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#3700NGD Silver Standard (bottom) 3 oz
$69.00

“it’s amazing! I trust in its power & performance.” - Gary Player, Golf Legend
Pathophysiology

• Primarily a disease of cartilage
• Cartilage made up of water, proteoglycans and collagen
• Mechanical stress across joints may initiate process followed by cartilage degradation
• Ultimate loss of joint architecture
Osteoarthritis = Joint failure
Treatment of OA

• Correct diagnosis
• Psychological factors
• Physical factors
  – Weight loss
  – Exercise
  – Formal PT
  – Neoprene sleeves
  – Other braces
  – Canes, etc

• Analgesia
  – Acetaminophen
  – NSAIDs
  – Opioids

• Intraarticular injection
  – Steroids
  – Hyaluronic acid

• Surgery