

Thank you for attending

Rheumatoid Arthritis and Osteoarthritis Treatment

*A CHAMPS webcast presented by
Dr. David Collier
on Thursday, November 3rd, 2005*

SUPPLEMENTARY INFORMATION PACKET

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Association of Mountain/Plains States)**
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PRESENTATION SLIDE TEXT (NOTES PAGES)

MANAGEMENT OF RHEUMATOID ARTHRITIS

RA: Observations

- RA affects 1% of the adult population
- >70% of patients develop joint damage or erosions within 2 years of the onset of disease (chronic, polycyclic course)
- >33% of patients are work disabled at 5 years
- >50% of patients will be functional Class III or IV within 10 years of disease onset
- If untreated, RA can result in joint destruction, deformity, disability, and premature death

RA: Challenges

- Preconceived notions that RA is a disease of lesser significance ("it's just arthritis")
- Lack of appreciation of the potentially severe prognosis (disability and early mortality) may delay diagnosis, referral, and treatment
- Delay in treatment may be due to lack of experience with prescribing and monitoring disease-modifying antirheumatic drugs (DMARDs)
- Primary care physicians are important members of the RA management team
- Early recognition of the signs and symptoms of RA followed by expedited diagnosis and treatment results in more favorable patient outcomes

ARA 1987 Criteria for RA (4 of 7 required)

- Morning stiffness >1h, present for at least 6 wk
- Swelling of 3 or more joint areas for at least 6 wk
- Swelling of wrist, MCP, or PIP; >6wk
- Symmetric joint swelling
- Rheumatoid nodules
- Serum rheumatoid factor (RF)
- Hand radiographic changes: erosions

Criteria were not intended for the diagnosis of RA in the clinical setting, particularly early disease

Suspicion of an Inflammatory Arthritis

- Spontaneous onset of 1 or more swollen joints
- Morning stiffness lasting > 45 minutes
- Diffuse joint pain and tenderness, particularly involving the MCPs and MTPs (forefoot pain can be the first and only small joint complaint)
- Marked fatigue
- Onset in women in the first year postpartum

Screening Tool for Inflammatory Arthritis (RA) in Primary Care

- Significant discomfort with squeezing the MCP and MTP joints
- Presence of 3 or more swollen joints
- More than 1 hour of morning stiffness

Emery P et al. *Ann Rheum Dis* 2002;61:290-297.

Anti-Cyclic Citrullinated Peptide Antibodies (Anti-CCP)

- RF not very specific for RA
- Autoantibodies reactive with synthetic peptides containing the unusual amino acid *citrulline* (modified arginine residue) are specifically present in the sera of RA patients:
 - Anti-CCP: sensitivity 56%, specificity 90%
 - IgM RF: sensitivity 73%, specificity 82%
 - RF and anti-CCP: sensitivity 48%, specificity 96%
- The presence of RF with anti-CCP are associated with a higher probability of joint damage and disability

Bas S et al. *Rheumatology* 2003;42:677-680.

RA: Poor Prognostic Indicators

- Earlier age at onset

- Polyarticular synovitis (>20 joints)
- Rheumatoid nodules
- High titer rheumatoid factor, possibly anti-CCP
- Elevated ESR or CRP level
- Erosions or cartilage loss on x-ray
- HLA-DR4 or "shared epitope"
- Extraarticular manifestations

Furst DE. *Rheum Dis Clin North Am* 1994;20:309-319.

RA: Extraarticular Manifestations

- Rheumatoid nodules
- Sjögren's syndrome
- Episcleritis or scleritis
- Interstitial lung disease
- Pericardial disease
- Systemic vasculitis
- Felty's: RA, neutropenia, splenomegaly

RA: Important Lessons

- Inflammation can be suppressed in early RA
- When inflammation is suppressed, patients benefit
- More therapy is not necessarily more toxic
- Long-term benefits may be derived from early therapy

RA: Initial Treatment

- NSAIDs: reduce joint pain and swelling; improve function (cost, GI tolerance, half-life, patient preference)
- Multidisciplinary care:
 - Rheumatology consultation
 - Physical and occupational therapy
 - Podiatry
 - Orthopaedics
- Glucocorticoids ?
- DMARDs: *start within 2-3 months of diagnosis* (shown to be the window of opportunity to prevent more joint destruction and preserve function)

Lard LR et al. *Am J Med* 2001;111:446.

RA: Glucocorticoids

- Local injection: limited to a few joints
- Low-dose oral (<10 mg prednisone):
 - "Bridge-therapy" until DMARD response (polyarticular synovitis)
 - Control of disease despite NSAIDs and adequate trials of DMARDs
 - Loss of independence or employment; flares; special events
 - Elderly - lower threshold for use
 - Toxicity (osteoporosis): dose and duration
- Triamcinolone acetonide (Kenalog): 60 mg IM prn flare

An Approach to Selecting DMARDs

- Patient compliance and convenience
- Cost of the DMARD and monitoring
- Time until expected benefit
- Potential for adverse reactions
- Comorbid diseases
- Response and toxicity to previous Rx
- Severity and prognosis of the disease
- Physician confidence in administering and monitoring the drug

An Approach to Selecting DMARDs

- Milder RA with no or few "poor prognostic indicators" consider:
 - Hydroxychloroquine (HCQ)
 - Sulfasalazine (SSZ)

- Severe RA with “poor prognostic indicators” consider:
 - Methotrexate (MTX) with rapid dose escalation
 - Combination DMARD therapy
 - New DMARDs and Biologics
- For women of childbearing age, effective contraception is required

Methotrexate (MTX)

- Fast acting: response in 3-6 weeks
- Not remitting: RA flares if drug d/ced
- Dosage:
 - Administer on a *weekly* basis, in one dose or cycled over 24 h
 - 5.0 or 7.5 mg po or SC/IM weekly, escalate rapidly to 15 mg/wk within 4-6 weeks and ideally to 20 mg/week by 8-12 weeks
 - Oral absorption is variable: if ineffective without rise in the MCV, try SC route

MTX: Side Effects and Toxicity

- Common:
 - Stomatitis, GI intolerance: try folate 1-2 mg/day
 - Myelosuppression: risks - use of antifolates, folate deficiency, renal insuff; use folate for rising MCV or MCV >100
 - Transient LFT abn: hold or reduce dose for levels >2-3 x nl
- Uncommon:
 - Hepatic fibrosis or cirrhosis (rare)
 - Pneumonitis: 2-6%
 - CNS reactions
 - Accelerated nodulosis
 - Fever, weight loss syndrome
 - Cutaneous vasculitis
 - Pneumocystis, fungal infections
 - ? Lymphoma association

Methotrexate

- Monitoring:
 - Baseline CXR, hepatitis B and C serologies
 - CBC, LFTs - 1 wk after 1st dose (idiosyncratic reaction)
 - CBC, Plt, AST/ALT, Alb, Cr q 4-8 weeks
- Contraindications / Precautions:
 - Chronic renal insufficiency
 - Significant pulmonary disease
 - Alcohol abuse (no > few drinks/month), liver disease, obesity, diabetes
 - Concomitant antifolate therapy
 - Pregnancy and lactation

RA: Monitoring Activity and Treatment

- Each visit:
 - Degree of joint pain
 - Duration of morning stiffness
 - Severity of fatigue
 - Active synovitis on exam by joint count
 - Limitation of function
 - Extraarticular manifestations
 - Adverse drug reactions
 - Health Assessment Questionnaire (HAQ) can be used to score the patient's function
- Periodically:
 - Disease progression on PE: loss of motion, instability, malalignment, and/or deformity
 - ESR or CRP elevation
 - Progression of radiographic damage of involved joints (hands and feet) every 1 to 2 years (joint exam may not adequately reflect disease activity or structural damage); x-ray, possibly by ultrasound or portable MRI

RA: Active or Progressive Disease Despite Current Treatment

- Rheumatology consultation
- Local glucocorticoid injection
- Change drug regimen:
 - Increase DMARD dosage
 - Change the DMARD
 - Add a DMARD (combination therapy)
 - Start or increase glucocorticoids (eval and treat secondary osteoporosis)
- Physical / Occupational Therapy
- Surgical options for mechanical symptoms

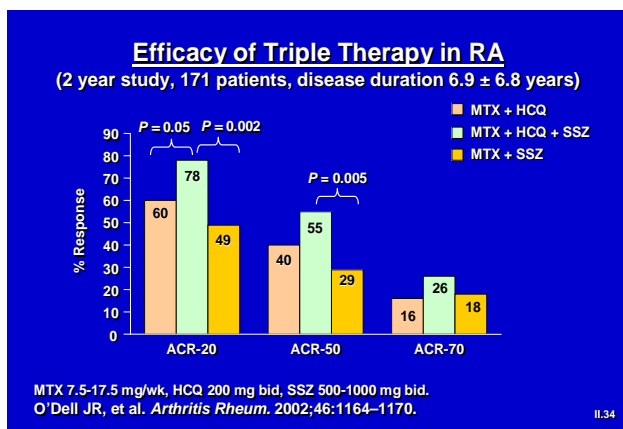
Refractory Rheumatoid Arthritis

- Rheumatology consultation
- Combination therapy: MTX/HCO, MTX/SSZ, MTX/SSZ/HCO, MTX/CSA, MTX/Leflunomide
- Cyclosporine A (CSA)/Neoral: 2.5-4.0 mg/kg/day
- Leflunomide (Arava)
- Etanercept (Enbrel), Infliximab (Remicade), Adalimumab (Humira)
- Anakinra (Kineret)
- Mycophenolate (CellCept): 1000 mg bid
- Cyclophosphamide, chlorambucil
- Investigational pharmacological or biological agents (anti-CD20, anti-CD40-L, CTLA4Ig)

ACR-20/-50/-70 Response Criteria

A 20%, 50%, or 70% improvement in:

- Swollen joint count, AND
- Tender joint count, AND
- At least three of the following:
 - Patient's global assessment of disease activity
 - Physician's global assessment of disease activity
 - Patient's assessment of pain
 - Acute-phase reactants (ESR or CRP)
 - Patient's assessment of disability (HAQ)

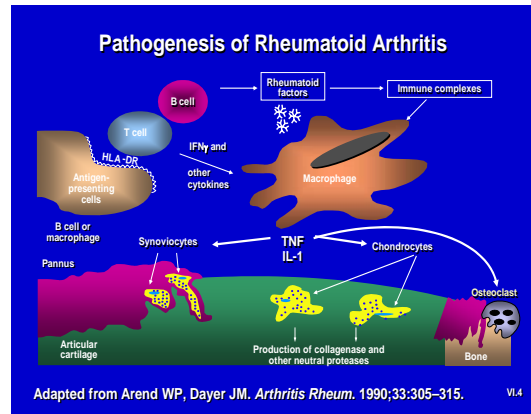
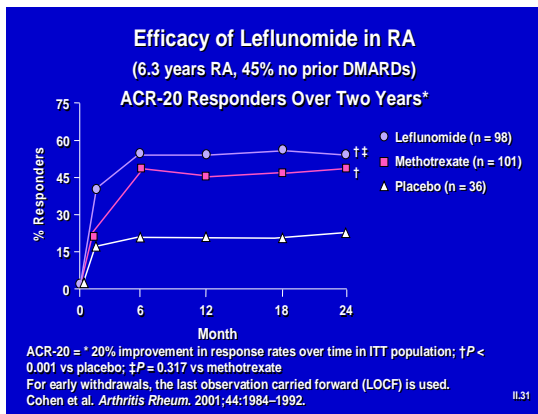


Newer Agents for the Treatment of RA

- Leflunomide (Arava)
- Anti-TNF agents:
 - Etanercept (Enbrel), 1998
 - Soluble TNF receptor
 - Infliximab (Remicade), 2000
 - Chimeric anti-TNF antibody
 - Adalimumab (Humira), 2002
 - Human anti-TNF antibody
- Anti-IL-1 agent:
 - Anakinra (Kineret), 2001
 - Modified IL-1 receptor antagonist (IL-1Ra)

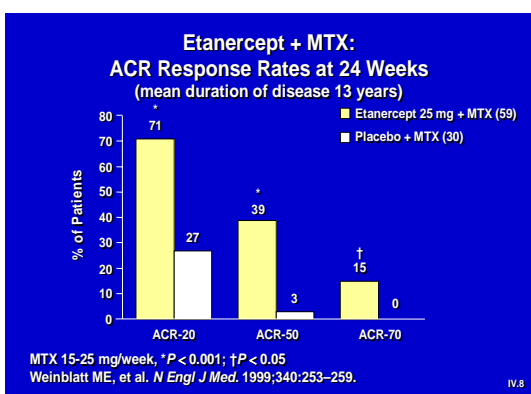
Leflunomide (Arava)

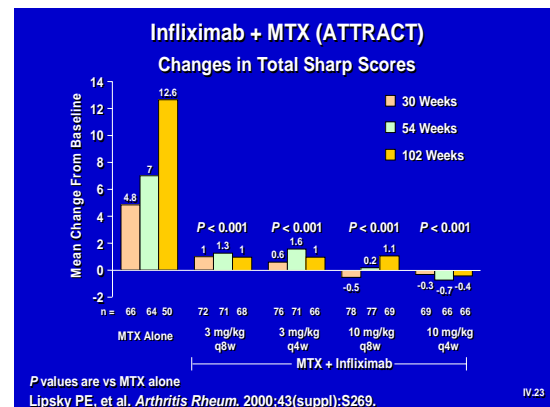
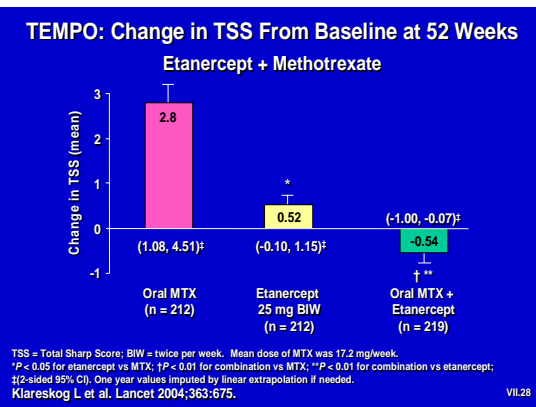
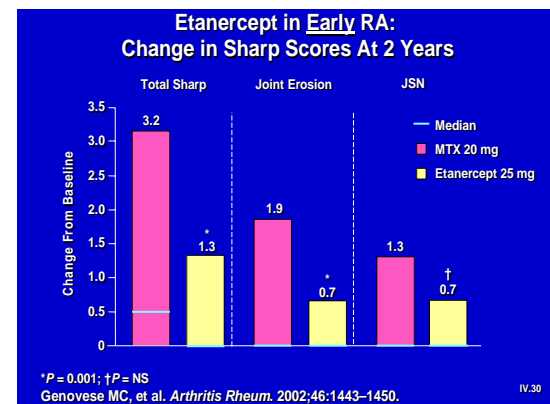
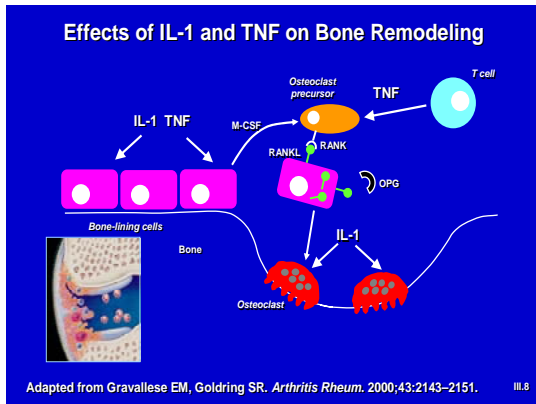
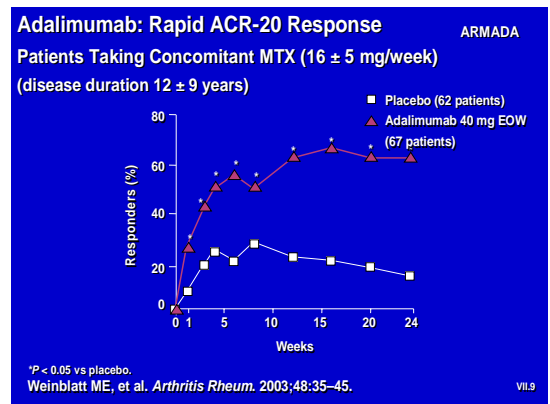
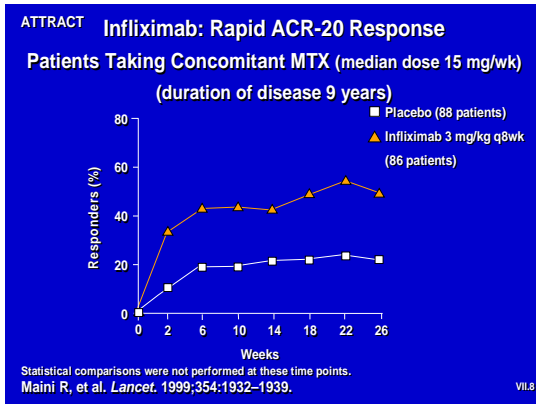
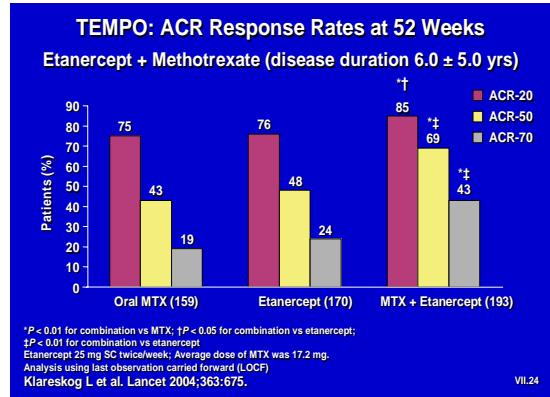
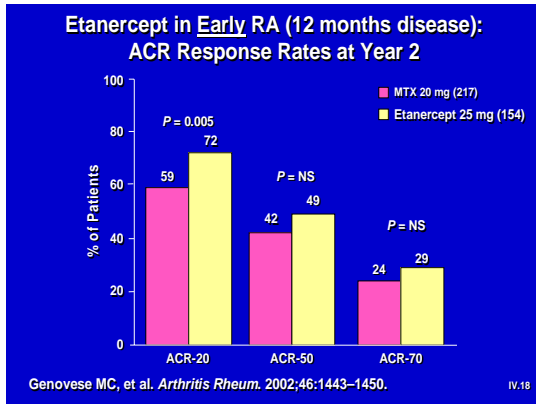
- Mechanism of action:
 - Prodrug: metabolite inhibits dihydroorate dehydrogenase required for pyrimidine nucleotide synthesis
 - Antiproliferative effects on T cells and anti-inflammatory effects
- Onset of action:
 - 4-12 wks, maximum effect by 4 months
- Dosage:
 - Loading dose: 100 mg qd x 3 (optional)
 - Maintenance dose: 10-20 mg qd
- Side Effects and Toxicity:
 - Increased LFTs/: usually < 2x increase and reversible; >3x (7%) increase requires discontinuation, dose reduction, cholestyramine if persistent
 - Hepatic failure: rare reports
 - Diarrhea (28%)
 - Rash (15%), reversible alopecia (9%)
 - Teratogenesis (Pregnancy Category X):
 - Men or women who wish to have a child: stop leflunomide, cholestyramine 8 grams tid for 11 days, verify plasma (M1) levels < 0.02 mg/L by 2 separate tests 14 days apart (without cholestyramine - 2 yrs to eliminate drug)
 - Bone marrow suppression/aplasia: rare
 - Serious infection or lymphoma risk unknown
- Monitoring:
 - LFTs, CBC, Cr q 4 wks x 6 months, then q 4-8 wks; baseline hepatitis serologies
- Contraindications / Precautions:
 - Pregnancy and lactation
 - Renal or hepatic insufficiency
 - Severe uncontrolled infections or immunodeficiency
 - No vaccinations with live virus
 - Rifampin (40% ↑ M1 levels), MTX: possible hepatic toxicity
 - ↑ NSAID and tolbutamide levels *in vitro*

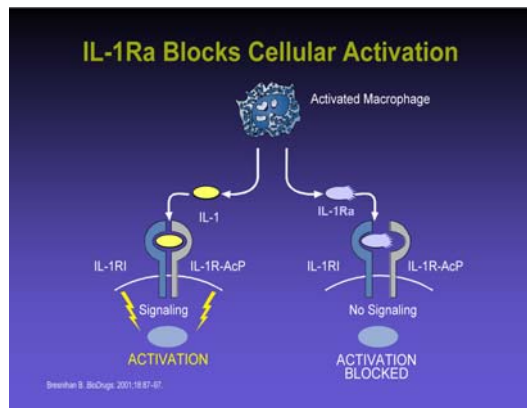
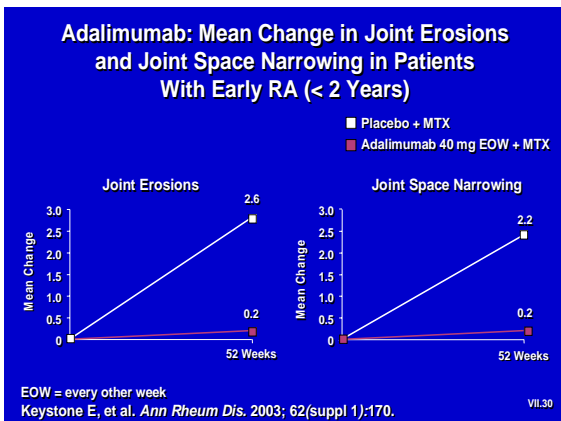


Characteristic	Etanercept (ENBREL®)	Infliximab (REMICADE®)	Adalimumab (HUMIRA™)
Class	sTNFR	TNF MAb	TNF MAb
Construct	Recombinant fusion protein	Chimeric MAb	Recombinant human MAb
Half-life	4 days	8-10 days	10-20 days
Binding target	TNF/LTα	TNF	TNF
Administration	25 mg SC 2x week or 50 mg SC once weekly	3-10 mg/kg IV with MTX Every 4-8 weeks	40 mg SC Every other week*

*Some patients not taking concomitant MTX may derive additional benefit from increasing the dosing frequency of adalimumab to 40 mg every week.

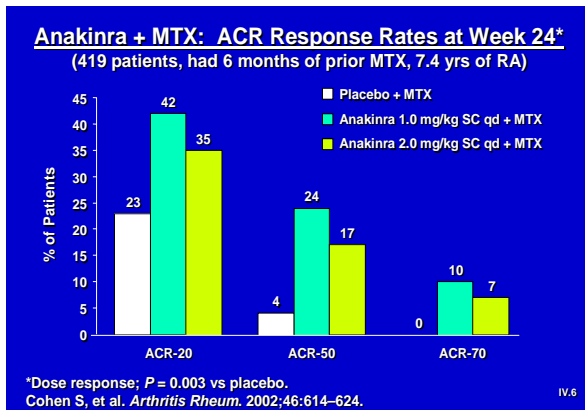






Anakinra (Kineret)

- Dosage:
 - 100 mg daily subcutaneous injection: half-life 4-6 hours
 - Predominantly cleared by the kidney: clearance ↓ in chronic renal insufficiency
- Side Effects and Toxicity:
 - Injection-site reactions: 71%; placebo 28%
 - Serious infections: 2%; placebo <1%
 - Use with TNF blocking agents not recommended: serious infections 7%; neutropenia 3%
 - Rare hypersensitivity reactions



Anti-TNF Therapy: Adverse Effects

- Injection site reactions, infusion reactions
- Serious infections: d/c drug in the setting of an active infection
- Atypical infections:
 - Tuberculosis: need pre-treatment PPD and CXR
 - Atypical mycobacterial infections
 - Candidiasis
 - Aspergillosis, Nocardiosis, Pneumocystis
 - CMV, Cryptococcosis, Coccidioidomycosis
 - Histoplasmosis: ? use in endemic areas
 - Listeria: avoid unpasteurized milk products, heat ready-to-eat meats
- Demyelinating disease
- Neoplasia:
 - Lymphoma: reported cases, difficult to ascertain increased drug risk over risk with RA alone (SIR 2.5)
 - Solid Tumors: limited data - risk unclear but does not appear to be increased, use with caution with h/o malignancy
- Cytopenias
- Heart failure
- Antibody production:

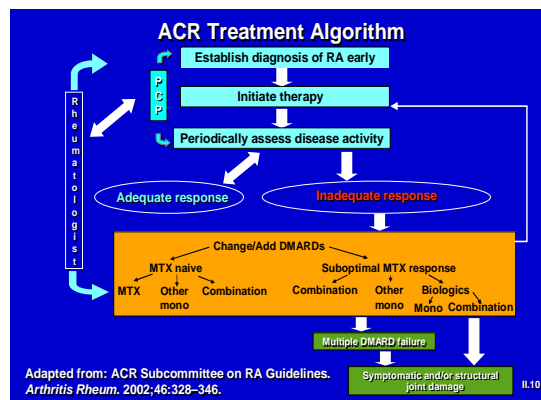
- o Non-neutralizing antibodies to the drug; incidence decreased with concomitant MTX therapy
- o ANAs and anti-ds-DNA antibodies (10%-50%), rare cases of drug-induced lupus

Average Costs of DMARDs

Drug	Dose	AWP/ mos	AWP/ year
MTX	15mg/wk	\$72	\$936
Leflunomide	20mg/day	\$422	\$5,064
Etanercept	25mg twice weekly	\$1,370	\$16,440
Infliximab	300mg infusion		\$16,660 (8 doses)
Adalumimab	40mg qowk	\$1,370	\$16,440
Anakinra	100mg/day	\$1,303	\$15,636

RA: Health-Care Maintenance

- Osteoporosis:
 - o Calcium / Vit D: 1500 mg /400-800 U/day
 - o Bisphosphonates
 - o DEXA scans
- Cardiovascular disease: assess risk / modify
- Smoking cessation
- Infection risk (particularly pulmonary infections):
 - o Influenza vaccination yearly
 - o Pneumococcal vaccination: before MTX



Rational Approach to DMARD Therapy in Severe RA

- Start oral methotrexate (unless contraindicated) with rapid dose escalation, consider low-dose steroid "bridge therapy"
- Inadequate response: consider parenteral (sq) methotrexate
- Inadequate response: MTX combination DMARD therapy [SSZ, HCQ, or leflunomide (risk of hepatotoxicity)] or change to leflunomide
- Inadequate response: add etanercept, infliximab, adalimumab, or anakinra

RA: Unanswered Questions

- How do we select the best DMARD for each patient (identify predictors)?
- Should we step-up or step-down initial DMARD therapy (combo rx)?
- Is there a role for induction therapy with steroids and/or anti-TNF / anti-IL-1 agents?

TOPICS OF LECTURE

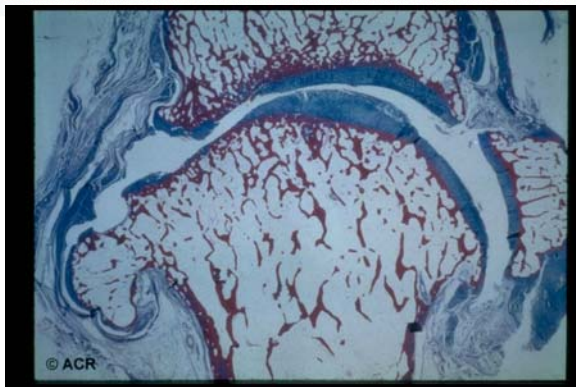
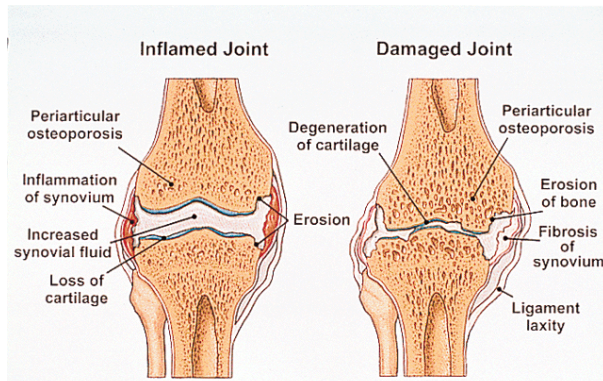
OSTEOARTHRITIS

- Definition
- Laboratory Tests
- Risk Factors
- Management of OA

OSTEOARTHRITIS

Definition:

Osteoarthritis is a heterogeneous disease representing a final common pathway of biochemical, metabolic, physiologic, and pathologic changes characterized by loss of articular cartilage and remodeling of subchondral and marginal bone.



OA: LABORATORY TESTS

No specific tests

Synovial fluid analysis

1. Type 1 fluid, 200-1500 WBC, 20-50% polys.
2. Normal viscosity, glucose
3. Negative Crystal Exam

Laboratory tests in secondary OA

Investigational: Cartilage degradation products in serum and joint fluid.

1. Hyaluronic acid, fragments of aggrecan
2. Type II collagen
3. Cartilage oligomeric protein (COMP)

OA: RADIOGRAPHIC FEATURES

- Joint space narrowing
- Bony sclerosis
- Marginal osteophytes
- Subchondral cysts
- Altered shape of bone
- Malalignment
 - Nails the diagnosis.



OA: RISK FACTORS

- Age: 75% of persons over age 70 have OA, uncommon under age 40.
- Female sex
- Obesity
- Hereditary
- Trauma
- Neuromuscular dysfunction
- Metabolic disorders

OA: Clinical Syndromes - Six Types

- Primary generalized OA
- Inflammatory/erosive small joint OA
- Isolated nodule OA
- Unifocal large joint OA
- Multifocal large joint OA
- Unifocal small joint OA

Management of OA

- Establish the diagnosis of OA on the basis of history, physical and x-ray examinations
 - 1. Knee pain with radiographic OA can be due to patellofemoral disease, ligament strain, anserine bursitis, iliotibial band syndrome, referred from lumbosacral disease, etc.
 - 2. Hip pain could be trochanteric, iliopsoas, and ischial bursitis, referred back pain, sacroiliac disease, etc.

TWO APPROACHES TO THE MEDICAL MANAGEMENT

- Practical Guidelines-ACR Osteoarthritis Guidelines of OA of the Knee, the American Pain Society Guidelines to treat OA, or the EULAR 2003 Recommendations for Treating OA of the Knee
 - Based on evidence and expert opinion
- Pathophysiological approach to OA

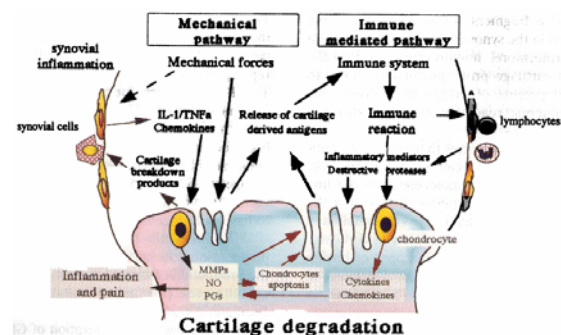


Figure 2. Schematic diagram of the involvement of mechanical and immune-mediated pathways in the cartilage degradation of osteoarthritis. IL-1 = interleukin-1; TNF α = tumor necrosis factor α ; MMPs = matrix metalloproteinases; NO = nitric oxide; PGs = prostaglandins.

WHAT IS IMPORTANT IN TREATING OSTEOARTHRITIS?

- Biomechanical or Biochemical targets?
- Primary Prevention?
 - Reduction of risk factors
 - 25% to 50% theoretically preventable by reducing obesity and repetitive activities.
- Secondary Prevention?
 - Interventions that prevent progression
 - DMOADs
- Tertiary Treatment?
 - Treatment of consequences of OA

OA: FIT TREATMENT TO THE PATIENTS

- Age
- Comorbidity
- Clinical Severity of OA
- Individual preferences
- Cost

OA: FIT TREATMENT TO THE PATIENT

- What are you treating-pain or limited motion?
- Discuss the patients concerns - clear up misconceptions
- Discuss what you can and cannot do for the patient
- Monthly telephone call to patient on stable treatment reduced joint pain
- Arthritis self-management education programs⁽¹⁾
(Self-help course of Arthritis Foundation)

¹ Arthritis Rheum 2003; 48:2207-2213

OA: MODIFICATIONS

- Weight loss if obese
- Modify activities and occupations
- Weight-bearing canes, braces and crutches
- Assistive devices - door handles, toilet seat extenders, special chairs, etc.
- Secondary fibromyalgia is common - correct sleep habits

OA: PHYSICAL THERAPY

- Heat (ultrasound, heat packs, wet heat) or ice
- Gait instruction
- Massage
- Balneotherapy
- TENS¹
- Exercise²

¹Clinical Rehabil 2002; 16:749-60

²J Rheumatol 2002; 29:1737-45

OA: Exercise^{1,2}

- Prescribe progressive exercise to:
 - o Improve general health
 - o Modify possible risk-factors in disease progression
 - o Increase ROM and flexibility
 - o Increase endurance and strength
 - o Reduce fall risk
 - o Chondroprotective

¹Current Rheumatology Reports 2001; 3:520-523

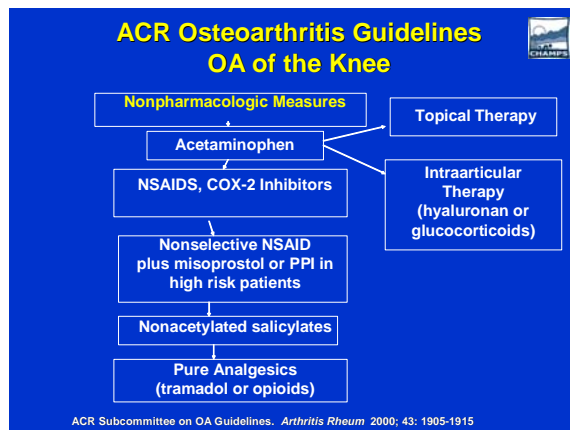
²J Rheumatol 2002; 29:1737-45

STRENGTHENING AND RECONDITIONING EXERCISE PROGRAM FOR OA

- Physical and Reconditioning Exercise Program for OA
- General program for muscle strengthening
 - o Warm up with ROM stretching
 - o Lift body part against gravity - 6 to 10 reps.
 - o Progressively increase resistance with weights or elastic bands
 - o Cool-down with ROM stretching
- Progress to aerobic exercise program

Table 4. Self-reported pain: standardized mean difference (SMD) and 95% confidence intervals (95% CI)

Study	Exercise (n)	Control (n)	Favours Exercise	Favours Control	SMD (95% CI)
Bautch, 1997	15	15	←		-1.20 (-0.41, -1.98)
Deyle, 2000	33	36	←		-0.93 (-0.43, -1.43)
Ettinger (A), 1997	144	75	←		-0.53 (-0.24, -0.81)
Ettinger (R), 1997	146	75	←		-0.36 (-0.08, -0.64)
Fransen, 2001	83	43	←		-0.62 (-0.24, -0.99)
Hopman-Rock, 2000	45	37	←		-0.20 (0.23, -0.64)
Kovar, 1992	47	45	←		-0.59 (-0.17, -1.01)
Maurer, 1999	49	49	←		-0.19 (0.21, -0.58)
Minor, 1989	49	19	←		-0.27 (0.27, -0.80)
O'Reilly, 1999	108	72	←		-0.32 (-0.02, -0.62)
Peloquin, 1999	59	65	←		-0.40 (-0.04, -0.76)
Rogind, 1998	11	12	←		-0.50 (0.33, -1.34)
Schilke, 1996	10	10	←		-1.06 (-0.11, -2.01)
Van Baar, 1998	54	59	←		-0.55 (-0.17, -0.92)
Overall	853	612	←		-0.46 (-0.35, -0.57)



PHARMACOLOGIC MANAGEMENT OF OA

- Topical agents
- Nonopioid analgesics
- NSAIDs and COXIBs
- Opioid analgesics
- Nutraceuticals and alternative therapies
- Intra-articular agents
- Experimental

TOPICAL AGENTS IN OA

- Counter irritants - Ben-Gay, Flexall 454, Icy-Hot, Mineral Ice, etc.
- Capsaicin - containing topicals
 - May paralyze C type pain fibers
 - Two studies support use in OA
 - Use daily, 4 times a day, for two weeks before benefit
 - Compliance poor without full instruction
 - Avoid contact with eyes
- Topical NSAIDs – Aspercreme, diclofenac
- Topical Glucosamine sulfate, chondroitin sulfate, and camphor
 - Recent blinded placebo controlled study showed improvement in knee OA in 4 weeks¹

¹J Rheumatol 2003; 30:523

ACETAMINOPHEN

1. First-line pharmacological agent in the treatment of patients with OA
2. Low incidence of adverse events and low cost
3. Introduced in Europe in 1893 by von Mering
4. Rapidly and completely absorbed from GI tract
5. Peak plasma concentration in about 30 to 60 minutes
6. Plasma half-life is 2 hours
7. No specific precautions in the elderly
8. Metabolism altered by severe acute or chronic liver disease
9. Watch out for acetaminophen containing products

ACETAMINOPHEN

Mechanism of Action

- Incompletely understood
- Inhibitor of **COX-3** in CNS
- Does not inhibit neutrophil activation
- In animal models inhibits substance P induced nociceptive response

CLINICAL TRIALS IN OSTEOARTHRITIS ACETAMINOPHEN

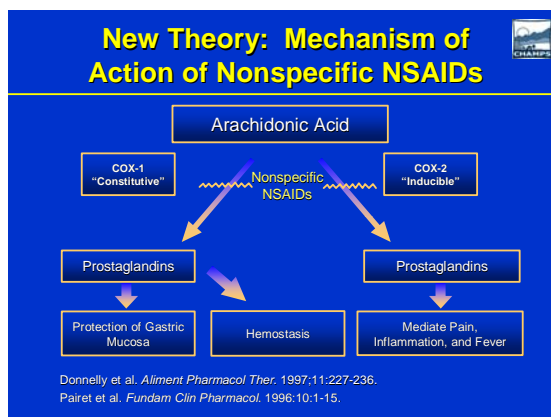
1. 1991 NEJM study by Bradley, Brandt, et.al.
 - Randomized, double-blind, 4 week study with 184 patients with OA of knee
 - 3 Groups - 2400mg or 1200mg of ibuprofen or 4,000mg APAP
 - Outcome

Variable (0-3)	APAP 4000mg	Ibuprofen 1200mg	Ibuprofen 2400mg	P value
HAQ Pain Score	0.33	0.30	0.35	0.93
Walking Pain Score	0.13	0.31	0.45	0.10
Rest Pain Score	0.06	0.33	0.40	0.05
Walking Distance Score	0.06	0.01	0.09	0.77

OA: NSAIDs

- Most widely prescribed drug class in country
- 1 in 7 Americans use NSAIDs, 17 million regular users, 50% over age 60.
- 111 million prescriptions annually. 3.9 billion dollars in annual costs.

- Beneficial effects of NSAIDs
 - Analgesia
 - Antipyresis
 - Anti-inflammatory
 - Decreases platelet aggregation



NSAIDs - CLASSIFICATION

- COX-1 specific - low dose aspirin
- COX nonspecific - Ibuprofen, Naproxen, Indomethacin, Sulindac, Piroxicam
- COX-2 preferential - Etodolac, Diclofenac, Nabumetone, Meloxicam
- COX-2 specific - Celecoxib, Rofecoxib, Valdecoxib

FACTORS AFFECTING THE CHOICE OF NSAIDs - THE DRUG

1. Efficacy
2. Tolerance / Safety
3. Dosage
4. Formulation
5. Cost

NSAIDs - EFFICACY

- No important differences with any NSAID
- Individual variations in response
- No correlation between amount of cyclooxygenase inhibition or plasma levels and efficacy
- COX-2 Specific Inhibitors: Celecoxib and formerly Rofecoxib, Valdecoxib
 - Comparable to Ibuprofen, Naproxen and Diclofenac
 - Suppresses animal models of inflammation
 - Indicated for OA, RA and Pain

TOXICITIES OF NSAIDS

- Hypersensitivity
- Gastrointestinal
- Nephrotoxicity
- Cardiotoxicity
- Hepatotoxicity
- Tinnitus / deafness
- Central Nervous Systems
- Cutaneous

HYPERSENSITIVITY REACTION AND THE COX-2s

HYPERSENSITIVITY

<u>Aspirin Sensitivity</u>	<u>Incidence</u>
Normal Subjects	0.09%
Chronic Rhinitis	1.4%
Nasal Polyps	14-23%
Asthma	3.8-28%
Asthma w/ Nasal Polyps	up to 78%

Celecoxib and Rofecoxib have generic NSAID warning
 (J Allergy Clin Immunol 2001; 108:47)

FIVE MAIN CATEGORIES OF REACTIONS TO NSAIDs

<u>Reaction Type</u>	<u>Underlying Diseases</u>	<u>Cross-Reactions</u>	<u>Reaction Mechanisms</u>	
			<u>Cox-1 Inhibition</u>	<u>Immunologic</u>
Cross-reacting respiratory	Asthma, polyps Sinusitis, rhinitis	ASA/NSAIDs	Yes	None
Cross-reacting urticaria	Chronic urticaria or none	ASA/NSAIDs	Yes	None
Urticaria/ anaphylaxis	None	None	No	IgE mediated
Aseptic Meningitis	None	None	No	DTH
Hypersensitivity	None	None	No	DTH

Manifestation of NSAID-Induced Upper GI Toxicity

- PUBs
 - perforations
 - ulcers
 - bleeds
- POBs
 - perforations
 - obstructions
 - bleeds
- Discomfort
 - dyspepsia
 - nausea
 - abdominal pain

GASTROINTESTINAL

- Gastritis, gastric ulcer, duodenal ulcers associated with NSAIDs
 - Endoscopic erosions in 10-30% of patients on NSAIDs
 - Ulcer complications 4%/year-most have no warning
- Diarrhea-especially with meclomen
- No protection from sucralfate and H-2 blockers
- Protection from misoprostol and pump inhibitors
- Poor PG inhibitors, such as sodium salicylate group (Disalcid, Trilisate) are easier on the stomach
- Cox-2 inhibitors similar to placebo on stomach

**Effects of ASA on
Anti-inflammatory Drugs: SUCCESS Trial**

UGI Safety	NSAIDs/ ASA	NSAIDs	Celecoxib/A SA	Celecoxib
UGI events/100 pt-yrs	(N=348)	(N=4046)	(N=697)	(N=8103)
Possible events	17.4	6.3	10	4.4
Ulcer complication	1.6	0.8	0.8	0.1
Ulcer complication/ Symptomatic ulcers	6.3	1.8	2.3	0.9

Ulcers were upper GI ulcer complications (perforation, gastric resection, bleeding, symptomatic upper GI ulcerations, or other GI events).

Addition of ASA to NSAIDs and coxibs increases adverse events
Smith et al. available at <http://www.nslar.org/abstracts/online.htm>

David H. Collier - 11/03/05

HIGH RISK PATIENTS FOR NSAID INDUCED ULCER

- Older Age
- Hx of PUD, GI BLEED
- Prior NSAID - related GI Intolerance
- Chronic Diseases (CAD, RA, COPD)
- Smoking, Ethanol USE
- Corticosteroids (≥ 10 mg)

- Anticoagulant Therapy
- Possibly H. Pylori Infection

CARDIOVASCULAR EFFECTS OF COX-2 INHIBITORS

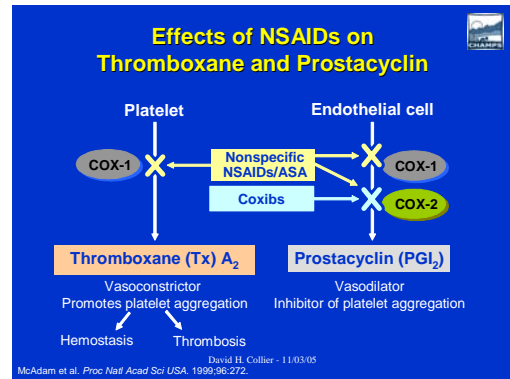
JAMA Article - August 22, 2001

Risk of Cardiovascular Events Associated With Selective COX-2 Inhibitors

Debabrata Mukherjee, MD
Steven E. Nissen, MD
Eric J. Topol, MD

ASPirin AND NONSTEROIDAL anti-inflammatory agents (NSAIDs) have proven analgesic, anti-inflammatory, and

Atherosclerosis is a process with inflammatory features and selective cyclooxygenase 2 (COX-2) inhibitors may potentially have antiatherogenic effects by virtue of inhibiting inflammation. However, by decreasing vasodilatory and antiaggregatory prostacyclin production, COX-2 antagonists may lead to increased prothrombotic activity. To define the cardiovascular effects of COX-2 inhibitors when used for arthritis and musculoskeletal pain in patients without coronary artery disease, we performed a MEDLINE search



Vioxx® Gastrointestinal Outcomes Research Trial

VIGOR Trial

Design

- Randomized, double-blind
- RA patients
- Median follow-up: 9.0 months

Treatments

- Rofecoxib 50 mg QD
- Naproxen 500 mg BID
- Low-dose aspirin excluded
- Antacids and OTC H₂-receptor antagonists allowed
- Acetaminophen, non-NSAID analgesics, glucocorticoids, and DMARDs allowed

Sample size

- 8,076 patients (4,047 rofecoxib; 4,029 naproxen)

David H. Collier - 11/03/05

Celecoxib Long-term Arthritis Safety Study

CLASS Trial

Design

- Randomized, double-blind
- OA/RA patients
- Conduct based on clinical practice norms
- Minimum 6 months' exposure

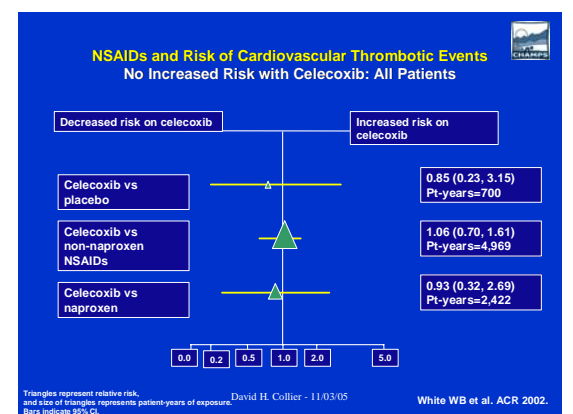
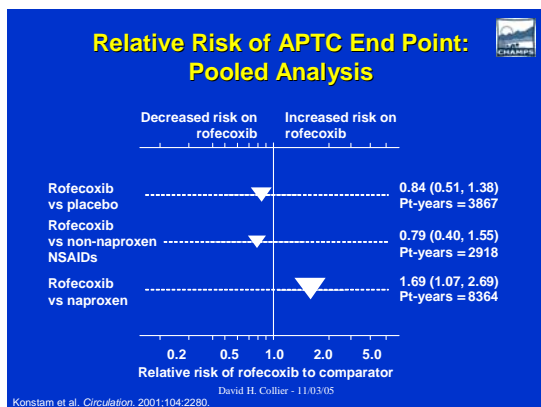
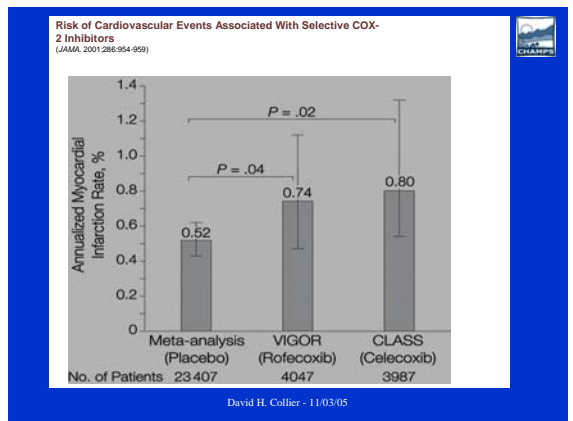
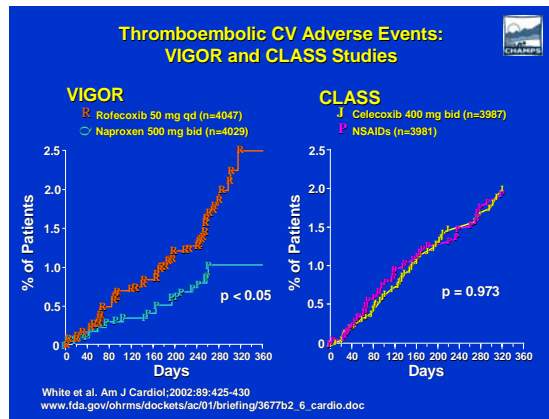
Treatments

- Celecoxib 400 mg BID
- Diclofenac 75 mg BID
- Ibuprofen 800 mg TID

Sample size

- 8,000 patients (4,000 celecoxib; 2,000 per NSAID); intent-to-treat analysis

Silverstein, et al. JAMA. 2000;284:1247-1255.
David H. Collier - 11/03/05



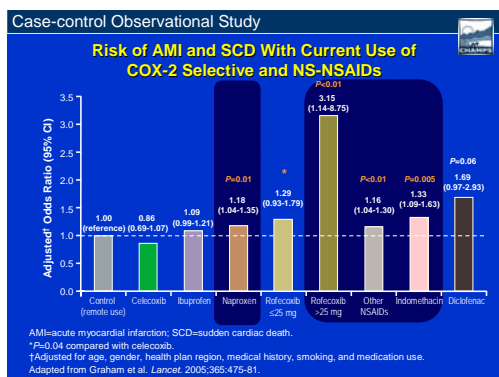
Cardiovascular Problems with NSAIDS

- **APPROVe study-Vioxx vs placebo in patients with colonic polyp history**
 - 2,600 pts, 25 mgs Vioxx, after 18 months
 - 45 pts CV events Vioxx, 25 pts CV events placebo
- **Adenoma Prevention Trial with Celecoxib or APC trial-NIH**
 - >2,000 pts, 400 mg, 800 mg Celebrex, > 33 month
 - CV events, placebo-6, 400mg-15, 800mg-20
- **Prevention of Spontaneous Adenomatous Polyps or PreSAP trial-Pfizer**
 - >1,500 pts, 400mg, >33 months
 - 400mgs (n=993) 16 events (1.7%), Placebo (n=628)11 events (1.8%)
- **Alzheimer's Disease Anti-inflammatory Prevention Trial (Adapt)**
 - Naprosyn more CV events, Celebrex and placebo the same.

FDA Kaiser Permanente Collaboration

- **Objectives**
 - Determine if risk of AMI and SCD is increased with NSAID or COXIB use
 - Compare risk of AMI and SCD between COXIBs: celecoxib and rofecoxib
- **Study Population**
 - California membership of Kaiser Permanente (KP)
 - All patients age 18-84 treated with coxib or NSAIDs from 1/1/1999 through 12/31/2001 (N = 1.4 million)
- **Methods**
 - Nested case-control study within this NSAID-exposed study cohort
 - Cases: All study cohort members with AMI or SCD during the study period
 - N=8,199 acute cardiac events (6,675 AMI: 1,524 SCD)
 - Controls: Risk-set matched 4:1 on event date, age, gender and health plan region

AMI=acute myocardial infarction; SCD=sudden cardiac death
Graham et al. Presented at ISPE 2004



Platelet and Cardiovascular Effects of COX-2 Specific Inhibitors

- COX-2 specific inhibitors spare platelets
- COX-2 specific inhibitors do NOT decrease cardiovascular risk
 - If have cardiovascular risk, do not use COXIBs
 - Celebrex behaves differently than Vioxx or Bextra
- Patients with cardiovascular risk need low-dose aspirin (≥ 81 mg/d) – use traditional NSAIDs with PPI
- All NSAIDs possibly could increase CV risk

RENAL EFFECTS OF COX-2 INHIBITORS

Intrarenal Functional Role of COX-2 vs COX-1

- COX-2 appears to be a dominant contributor to sodium chloride and water homeostasis.
- COX-1 appears to have a more dominant role in the maintenance of glomerular filtration rate.
- Nonetheless, functions of both COX enzymes appear to overlap.

Renal Syndromes Related to Use of Conventional NSAIDs

Fluid and electrolyte abnormalities

- Sodium chloride and water retention with edema formation (typically $\geq 5\%$)
- Hyperkalemia

Hypertension

- Interaction with antihypertensive drugs and diuretics

Congestive heart failure

- Fluid retention and interaction with diuretic drug treatment

Acute renal failure

- Hemodynamically mediated during decreased renal perfusion

Nephrotic syndrome

- Minimal change glomerulonephritis and interstitial nephritis

Papillary necrosis

- Acute (usually single-drug pathogenesis)
- Chronic (usually multi- drug pathogenesis)

HIGH RISK PATIENTS FOR RENAL TOXICITIES

- Older Age
- ASHD
- Renal Insufficiency
- Renal hypoperfusion states: CHF, Cirrhosis, diuretics, hypovolemia, nephrotic syndrome
- Risk factors for hyperkalemia: diabetes, renal insufficiency, ACE inhibitors, beta blockers, potassium sparing diuretics

NSAIDs

- Dosage - single and twice-a-day regimens have more compliance
- Formulation
 - Enteric coated - Ecotrin, Easprin, Diclofenac
 - Liquid - Ibuprofen, Naproxen, Trilisate
 - Slow release - Indocin SR, Voltaren XR, Naprelan, Oruvail
 - Injectable – Ketorolac (soon to see Paracoxib)
- Cost - use generic NSAIDs first if patient not at risk
 - COX-2 inhibitors more costly than traditional NSAID
 - Traditional NSAIDS plus H⁺ pump inhibitor may be less costly as pump inhibitors go generic.

NSAIDs - COX-2 Inhibitors

- Drug interactions
 - Can be used with warfarin
 - Increases methotrexate levels slightly
 - Have potential interactions with diuretics and ACE inhibitors, increase drug levels of lithium
 - Celecoxib contraindicated in sulfa allergic
- COX-2 inhibitors are not "super" aspirin but are a safer aspirin

NONOPIOID ANALGESICS IN OA

- Tramadol (Ultram)¹
- Tramadol and Acetaminophen (Ultracet)²
 - Affects U-1 opioid and serotonin pathways
 - Non ulcerogenic
 - May be added to NSAIDs, acetaminophen
 - Both forms studied in OA and found beneficial
 - Side effects: Nausea, vomiting, dizziness, drowsiness, rash, constipation and may lower seizure threshold

¹J Rheumatol 2002;29:2196-9

²Clin Ther 2002; 24:282-97

OPIOID ANALGESICS FOR OA

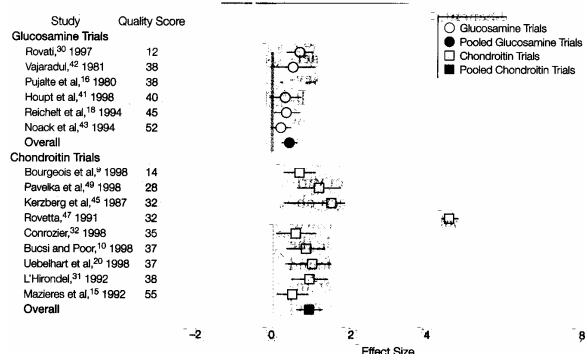
- Use after most other medical interventions tried
- Document decrease in pain level (VAS) and increase in function
- Follow routinely-watch for addictive behavior

- Contract your patients
 - State objectives for determining treatment success
 - You are exclusive supplier of drug
 - Can get urine-tox screen at any time
- Codeine, propoxyphene, hydrocodone, oxycodone, and long acting morphine all studied in OA
 - Only oxycodone and long acting morphine shown statistically better in blinded study than acetaminophen
 - Anticipate and prevent constipation
 - Watch for CNS effects in elderly
 - Long-acting oxycodone may have fewer CNS side effects
- Morphine and fentanyl patches for severe pain interfering with daily activity and sleep

NUTRACENTICALS IN OA

- Glucosamine and chondroitin sulfate marked in US as nutritional supplements for arthritis
- Popularized by Jason Theodasakis, MD in two books, "The Arthritis Cure" and "Maximizing the Arthritis Cure"
- www.Theo.com

Figure 1. Forest Plot of Effect Sizes for Trials and Pooled Effects



NUTRACEUTICALS IN OA - SUMMARY

- Glucosamine and chondroitin sulfate are orally absorbed and preferentially distributed to the joints
- Have analgesic effect in OA
- Onset of analgesia slower than NSAIDs
- Some evidence for "chondroprotection"
- Very safe. Dose of glucosamine is 500 mg TID, Chondroitin Sulfate 400 mg TID. If respond in two months may decrease dose.

INTRA-ARTICULAR AGENTS

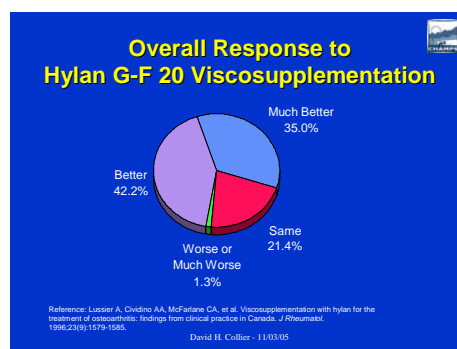
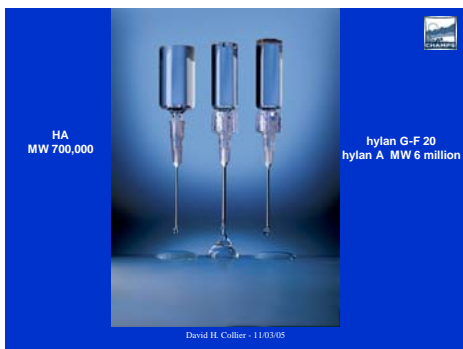
- **Corticosteroids**¹
 - Two year, double-blinded study of every 3 months injection of steroid or placebo
 - Significant pain relief
 - No difference in joint space width
- **Hyaluronate**
- **IL-1ra (Kineret)**²
 - 14 patients injected with 150mg of IL-1ra
 - Dramatic improvement in pain at one month
 - No side effects

¹ Arthritis Rheum 2003; 48:370-77

² ACR Annual Scientific Meeting - Late Breaking Abstract - 10/28/03

HYALURONAN OR VISCOUSUPPLEMENTATION IN OA

- Hyaluronic acid (HA) is polysaccharide made up of N-acetyl glucosamine and glucuronic acid and is core protein of proteoglycans
- Exhibits elastic and viscous properties - slow movement HA is viscous, fast movement HA is elastic
- When injected HA disappears from joint in less than a week
- HA induces the formation of endogenous HA
- HA has anti-inflammatory effects
- Human and animal studies show prolonged analgesia after a series of HA injections



CAVEATS ABOUT HYALURONAN IN OA

- The cross linked product (Synvisc) has been reported to be associated with rare post injection flares
- About 2.7% of patients develop local adverse reactions
- Crystalline induced flares have been described post injection
- Both products are isolated from rooster comb. Patients who are allergic to chickens or eggs should not receive therapy
- No studies of repeated series of injections reported
- Cost of therapy is \$500-\$800 (HA product, visit, injection) and is reserved for those who failed conventional therapy
- Only approved for use in knee but studied in shoulder and ankle

SURGICAL INTERVENTIONS IN OA

- Tidal joint irrigation
- Arthroscopic examination
- Reparative
- Reconstructive
- Joint Replacement

Complimentary and Alternative Therapy in Patients with OA

- Use of Alternative Therapy is Common in OA¹
 - 4 Ethnic groups studied for use of alternative therapy (AT)
 - African-Americans – 85%
 - Asian – 87%
 - Caucasian – 79%
 - Hispanic –81%
 - Dietary changes were the most common AT

¹Arthritis & Rheum 2003; 48(9Supp):S488

ALTERNATIVE THERAPIES IN OA

- Leech therapy¹
- S-adenosylmethionine (SAME)²
- Ginger extract³
- Avocado/Soybean Unsaponifiables⁴
- Acupuncture^{5,8}
- Electromagnetic Fields⁶
- Magnets⁷

¹ Ann Intern Med 2003; 139:724-730

² J Fam Pract 2002; 51: 425-30

³ Arthritis Rheum 2001; 44:2531-8

⁴ Arthritis Care & Research 2002; 47:50-8

⁵ Acupuncture Med 2002; 2019-21 & BMC Complement Altern Med 2002; 2:3

⁶ Cochrane Database Syst Rev 2002; 1:CD003523

⁷ Curr Med Res Opin 2001; 17:190-6 & Altern Ther Health Med 2002; 8:50-5

⁸ Arthritis & Rheum 2004; 50(9supp):S644

Pulsed Electrical Stimulation (Bionicare Device) in Knee OA¹

- Pulsed Electrical Stimulation (PES) is a low frequency, low amplitude, voltage source, Monphasic, spiked signal to the knee via skin surface electrodes.
- Use for 6 or more hours per day
- Showed mild but statistically significant improvement in physician's global evaluation, patient's evaluation of pain, and patient's evaluation of function of the treated knee.¹
- Mild skin reactions (thought to be to the gel) in 24%
- The main author of the study was Thomas Zizic

J Rheumatol 1995;22:1757-61

OA: MANAGEMENT SUMMARY

- First be sure the pain is joint related
- Discuss disease and concerns of patient
- Initial treatment
 - Modifications - weight loss, modify activities and occupations, assistive equipment
 - Strengthening and reconditioning program
 - Topical agents and local heat or ice
 - Acetaminophen

OA: MANAGEMENT SUMMARY

- Second-line approach
 - NSAIDs
 - Nutraceuticals - glycosamine and chondroitin sulfate
 - Intra-articular agents or lavage
 - Steroids
 - Hyaluronan
 - Tramadol or Opioids
 - Alternative Therapies
- Third-line
 - Arthroscopy
 - Osteotomy
 - Total joint replacement

ADDITIONAL NOTES:

Biography of Dr. David Collier

Dr. David H. Collier is the Chief of the Division of Rheumatology at Denver Health Medical Center, and a Professor of Medicine at University of Colorado Health Sciences Center. He received a Bachelor of Science degree from California Institute of Technology in Pasadena, California, and his MD from the Washington University School of Medicine in St. Louis Missouri. Since his graduation, Dr. Collier has been a prolific researcher, writer, and presenter. He received an Excellence in Teaching Award from the Medical Student Council at the University of Colorado Health Sciences Center in 1998, received the 6th Annual Faculty Outstanding Clinician Award of the Year in 2000 by the Denver Health and Hospital Medical Staff, and was given the Rocky Mountain Chapter of the Arthritis Foundation Physician of the Year Award in 2005. Dr. Collier currently serves on the Board of Directors for the Rocky Mountain Chapter of the Arthritis Foundation, and acts as Chairman of their Patient Advocacy Committee.

Description of CHAMPS

CHAMPS, the Community Health Association of Mountain/Plains States, is a non-profit organization dedicated to providing a coordinating structure of service to non-profit primary health care programs whose primary purpose is to serve the medically indigent and medically underserved of Region VIII (CO, MT, ND, SD, UT, and WY). CHAMPS also serves the Region VIII State Primary Care Associations that assist those nonprofit primary health care programs. Currently, CHAMPS programs and services focus on education and training, collaboration and networking, policy and funding communications, and the collection and dissemination of regional data for Region VIII Community Health Centers and Primary Care Associations.

For more information, please visit www.champsonline.org or call (303) 861-5165.

Description of the Arthritis Foundation

The Arthritis Foundation exists to help clinicians help their patients. The Arthritis Foundation supports research, and offers a wide variety of classes, presentations, and free lectures to provide information and instruction that can help people with arthritis take control and ensure high quality of life. The mission of the Arthritis Foundation is to improve lives through leadership in the prevention, control, and cure of arthritis and related diseases. The Foundation is the only organization in the country committed solely to helping find a cure for this disease which is the leading cause of disability in the US, and to making life easier for those who are faced with the challenges of arthritis. The Rocky Mountain chapter, located in Denver, Colorado, serves the more than 1 million people with arthritis in Colorado, Wyoming, and Montana.

For more information, please visit www.arthritis.org or call 1-800-475-6447.