

Update on rheumatology - is this really EBM?

Community Faculty Development Symposium

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What we could talk about

- New insights into autoimmunity and apoptosis
- Rationale use of ANA testing
- Osteoporosis
- The many new biologics coming down the pipeline.

What we will talk about

- How to approach the problem of painful limbs.
- Why identify and treat rheumatoid arthritis early?
- TNF inhibitors in Rheumatoid Arthritis (RA)
- Are cox 2 selective inhibitors an advantage over less selective NSAIDs?

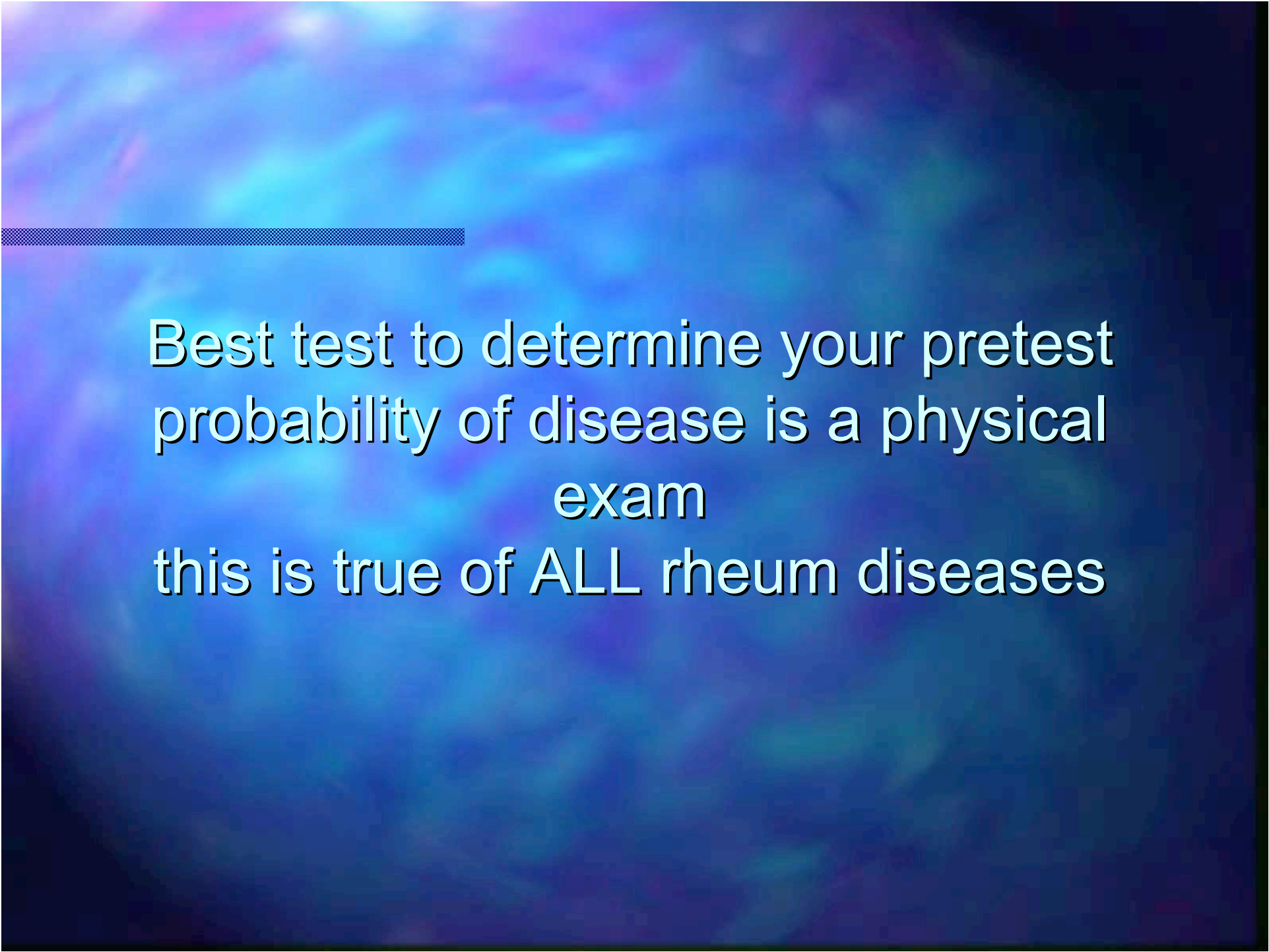
Our first case

- A 37yo woman is seen for 8 weeks of hand and foot pain. She is otherwise healthy, has 2 children ages 1 and 4. She takes no medicines, has had an appendectomy in the past, and is currently working part-time in her husband's computer business as a book keeper.

- She notes that the onset of pain was insidious. She thinks her hands might swell in the morning as she notes her rings are tight. She might be more tired than usual and is surprised that she is 3 pounds lighter than she thought she weighed. She denies a rash, cankers, chest pain, bowel changes, Raynauds, back pain, paresthesias, weakness. She is sexually active with her husband. She had no preceeding illness.



Now what do we do?



Best test to determine your pretest
probability of disease is a physical
exam
this is true of ALL rheum diseases

What to look for on exam

- Is it the joints? (nerve, muscle, bursa, tendons, bone, soft tissue)
- Which joints? (polyarticular, pauciarticular, monoarticular)
- Does it include the spine?
- Is there evidence of synovitis or bony enlargement or not sure?
- Are there clues from other parts of the exam?

The grand grid

■ Inflammatory

- Monoarticular - gout, hemarthrosis, pseudogout
- Pauciarticular - psoriatic, lyme IBD, RF, reactive
- Polyarticular - RA, SLE, DM, PM, SScI, chronic gout
- Spinal - ank spond, psoriatic arthritis, reactive arthritis

■ Degenerative

- Monoarticular - traumatic OA, PVNS
- Pauciarticular - OA of the hip, knee
- Polyarticular - nodal OA, hemochromatosis, cartilage issues
- Spinal - DDD, facet arthropathy, DISH

Physical exam

- Normal vital signs (no fever)
- Normal skin. No subcutaneous nodules
- Normal lungs, heart, abdomen, LN, thyroid, neurologic exam
- Joint exam shows mild synovitis of the MCP and PIP joints of the hand, the wrists and the MTPs of the feet.
- Therefore, she has a symmetrical, inflammatory polyarthritis.





What is the differential of early
synovitis?

Review of Early RA: Differential Diagnosis

- Viral arthritis
 - B-19 parvovirus, rubella, hepatitis C
- Lyme arthritis
- Reactive arthritis
 - eg, postinfective: throat, gut, sexually acquired
- Seronegative spondyloarthropathy
 - eg, psoriatic, ankylosing spondylitis, inflammatory bowel disease
- Connective tissue disease
 - eg, systemic lupus erythematosus (SLE), scleroderma, inflammatory osteoarthritis (OA)
- Regional pain syndrome/soft tissue RA

Brewer EJ Jr, et al. *Arthritis Rheum.* 1977;20(suppl):195-199.
Clinical Guidelines for RA. Scottish Intercollegiate Guidelines Network (SIGN).
Available at: <http://www.sign.ac.uk/guidelines/fulltext/48/index.html>.
Accessed November 2003.

Review of Early RA: Differential Diagnosis (cont'd)

- Polymyalgia rheumatica
- Polyarticular gout
- Fibromyalgia
- Pseudogout (chondrocalcinosis; calcium pyrophosphate dihydrate crystal deposition) and other crystal-induced arthropathies
- Medical conditions presenting with arthropathy
 - eg, sarcoidosis, thyroid disease, infective endocarditis, hemochromatosis, diabetic cheiroarthropathy, paraneoplastic syndromes, multiple myeloma

How can you be sure this is RA and not another process?

- RF?
- ANA?
- CCP? (cyclic citrullinated peptide)
- ESR, CRP?
- Rheumatology consult?
- Time?

The best test for early RA

- RF and CCP
- Sens IgM RF 73%, IgA RF 63%, CCP 56%
- **Spec IgM RF 82%, IgA RF 90%, CCP >90%**
- Combination best at spec 98%
- CCP +2% blood donors but not elderly
- Together, IgM RF and CCP predict more serious disease defined by erosions and by disability. No pt with all three markers had remission at 8yrs.
- Bas Anti-cyclic citrullinated peptide antibodies, IgM and IgA rheumatoid factors in the diagnosis and prognosis of rheumatoid arthritis Rheumatology 2003;42:677-680

Furthermore...

- CCP antibodies may be found in early disease (50-70%) with a spec with second generation tests of 95-98%. IgM RF may be positive but with less specificity.
- May precede the development of disease.
- 93% +CCP pts with UDPA progressed to RA while only 25% of CCP- pt prog.

Diagnostic Criteria for Early RA

- A set of 7 diagnostic criteria for early RA have been proposed that may distinguish between self-limiting arthritis and persistent erosive and nonerosive arthritis
 - Symptom duration at first visit
 - Morning stiffness ≥ 1 hour
 - Arthritis in ≥ 3 joints
 - Bilateral compression pain in metatarsophalangeal (MTP) joints
 - IgM-RF positivity
 - Anti-CCP positivity
 - Erosions on radiographs of the hands or feet

Visser H, et al. *Arthritis Rheum.* 2002;46:357-365.

Scoring system for early synovitis

■ Synovitis >6wks<6mon	■ 2.49 OR score 2
■ Synovitis >6 mon	■ 5.49 3
■ EMS > 1 hr	■ 1.96 1
■ Arthritis > 3 joint groups	■ 1.73 1
■ Bilateral MTP compression	■ 1.65 1
■ IgM RF >5 IU	■ 2.99 2
■ Anti-CCP >92 IU	■ 4.58 3
■ Erosions on hand or foot film	■ 2.75 2

Total score and probability of persistent vs self limited synovitis

■ 0 = .10

■ 1 = .15

■ 2 = .23

■ 3 = .34

■ 4 = .46

■ 5 = .59

■ 6 = .71

■ 7 = .80

■ 8 = .87

■ 9 = .92

■ 10 = .95

■ 11 = .97

■ 12 = .98

■ 13 = .99

LR - likelihood ratios

- $LR + = \text{sens}/(1 - \text{spec})$
- $LR - = (1 - \text{sens})/\text{spec}$
- Pre-test odds = $\text{prev}/1 - \text{prev}$
- Post-test prob = $\text{post-test odds}/(\text{post-test odds} + 1)$

Prevalence and LR effect on post-test probabilities

Pretest probability	Post-test prob +	Post-test prob -
25%	.80	.17
50%	.92	.29
75%	.97	.55

Prevalence and LR on post test probability

Pre-test prob	LR+ 12 Post-test prob	LR- .4 Post-test prob
25%	.80	.17
50%	.92	.29
75%	.97	.55

Now what to do?

- Add a NSAID
- Add a DMARD (disease modifying drug)
- Add prednisone
- See a consultant

What is the data that early treatment benefits RA?

- COBRA trial - SSZ vs high dose pred plus SSZ and MTX showed increasing radiologic benefit after 5 years despite similar clinical benefit.
- ERA trial - etanercept vs MTX which we will review later
- Fin-RACo - stepped down combination tx with SSZ, MTX, Prednisone and HCQ vs monotherapy with MTX.
- All suggest a window of opportunity to treat RA and diminish radiographic damage
 - Landewe RB COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefit of a brief intervention A&R 2002;46:347-56
 - Bathon JM A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis NEJM 2000;343:1586-93
 - Mottonen T Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis:a randomized trial. FinRACo trial group Lancet 1999;353:1568-73

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)

Sharp Scores

Erosion scores

- 17 joints of each hand/wrist
- 6 joints of each forefoot
- Scale: 0–5; Total score: 0–230

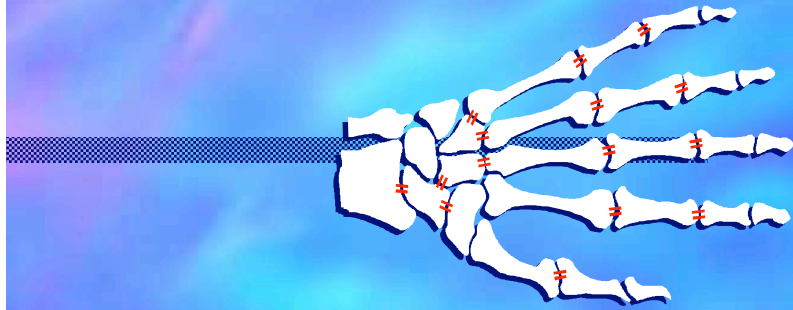
Joint space narrowing (JSN) scores

- 16 joints of each hand/wrist
- 5 joints of each forefoot
- Scale: 0–4; Total score: 0–168

Total Sharp score

- Add erosion and JSN scores
- Total score: 0–398

Modified Sharp Scoring Method

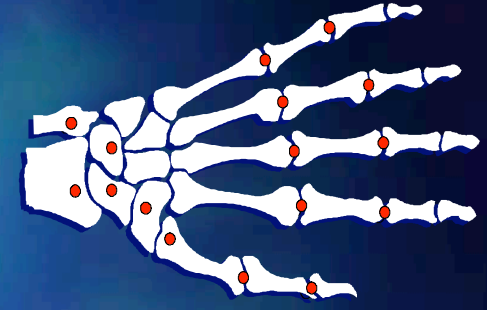


= Joint space narrowing (JSN)

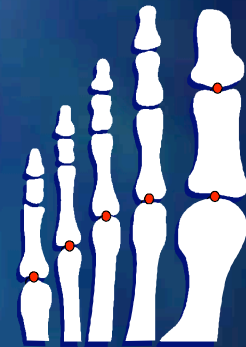


42 joints evaluated

JSN scale: 0 = normal
 1 = focal or doubtful
 2 = $\geq 50\%$ of original space left
 3 = $\leq 50\%$ of joint space or subluxation
 4 = bony ankylosis or luxation



• Erosions



44 joints evaluated

Erosions scale: 1 = discrete
 2–4 = depending on surface area involved
 5 = complete collapse

Health Assessment Questionnaire (HAQ)

Widely accepted, validated, rheumatology-specific instrument to assess physical function in RA

- Gold standard of OMERACT/FDA
- 20 questions covering eight types of activities
 - Dressing and grooming, arising, eating, walking, hygiene, reaching, gripping activities of daily living
 - A mean decrease of at least 0.22 in HAQ score is considered a minimum clinically important difference (MCID)

HAQ Disability Index (HAQ-DI)

- Scores the worst items within each of the eight scales
- Based on use of aids and devices

Buchbinder R, et al. *Arthritis Rheum.* 1995;38:1568–1580; Sullivan FM, et al. *Ann Rheum Dis.* 1987;46:598–600; Kosinski M, et al. *Arthritis Rheum.* 2000;43:1478–1487.

Fin RA Co

- Remission achieved in 24.7% of pts on combination therapy vs 11.2% of pts on SSZ alone after 1 year. (24/97 vs 11/98)
- At year 2, 37% remission vs 18.4%.
- Suggests that early aggressive treatment increases the chance of remission.

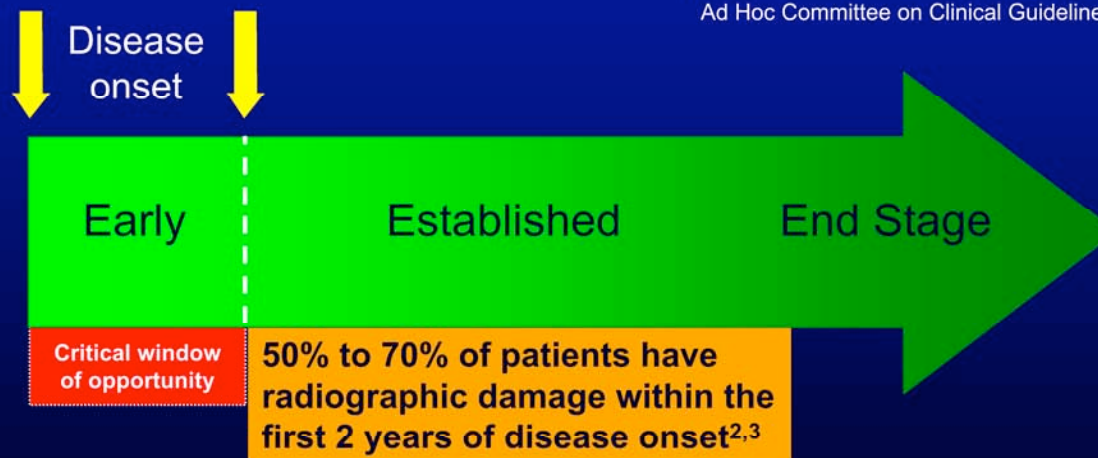
COBRA

- Looked at a step-down study of SSZ, MTX and prednisone vs SSZ alone.
- Again, although the clinical differences between the groups was unchanged at 1 year, there was a large difference in erosive scores in favor of combination therapy.

ACR Recommendations: Early Aggressive Treatment of RA

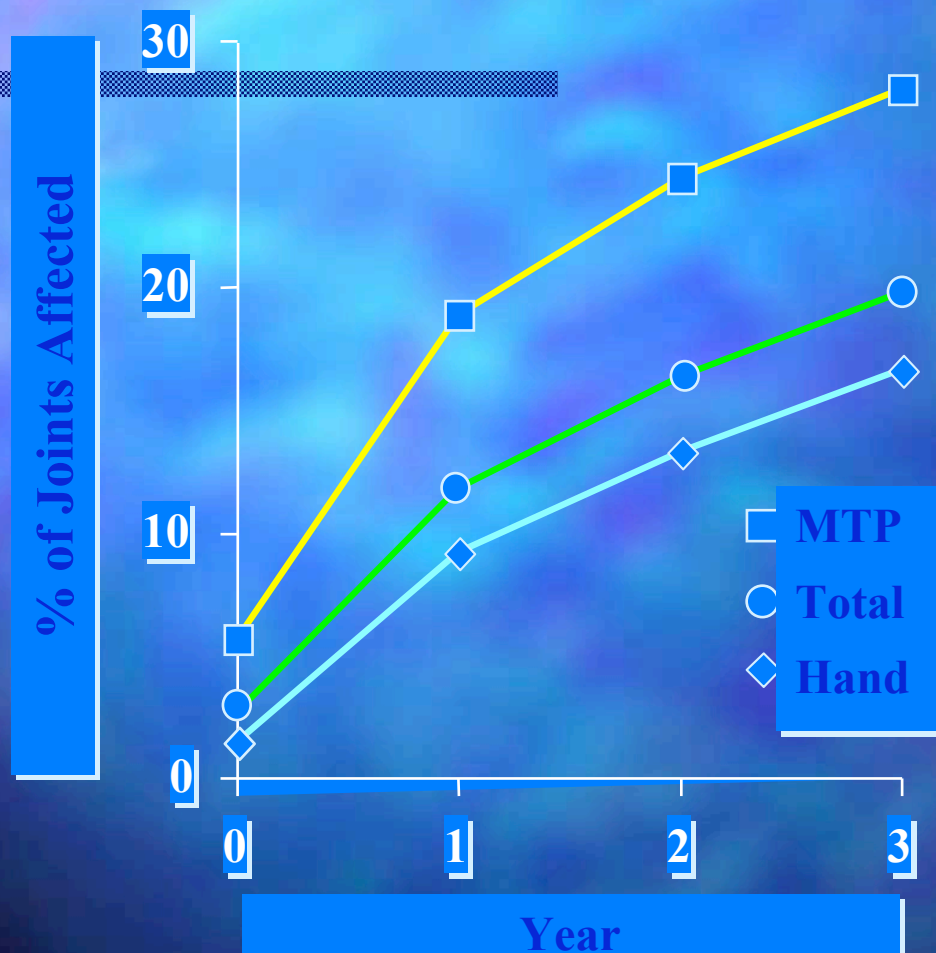
“Successful treatment to limit joint damage and functional loss requires early diagnosis and timely initiation of disease-modifying agents. The goal of treatment is to arrest the disease and achieve remission.”¹

American College of Rheumatology (ACR)
Ad Hoc Committee on Clinical Guidelines



1. ACR Subcommittee on Rheumatoid Arthritis Guidelines. *Arthritis Rheum.* 2002;46:341.
2. van der Heijde DMFM. *Br J Rheumatol.* 1995;34(suppl 2):74-78.
3. Sundy JS, St. Clair EW. *J Musculoskeletal Med.* 2002;19:395-403.

Joint Erosions Occur Early in RA



- Up to 93% of patients with < 2 years of RA may have radiographic abnormalities
- Rate of progression is significantly more rapid in the first year than in the second and third years
- Radiographic changes in the feet are important indicators of disease progression in RA

van der Heijde DM et al. *J Rheumatol.* 1995;22:1792–1796;
Fuchs HA et al. *J Rheumatol.* 1989;16:585–591; McQueen FM, et al.
Ann Rheum Dis. 1998;57:350–356.

Treatment: The Earlier, the Better

ACR-20 response criteria from 14 randomized, controlled trials of second-line drugs/devices; N=1435

Endpoint: To determine relationship between disease duration and response to treatment

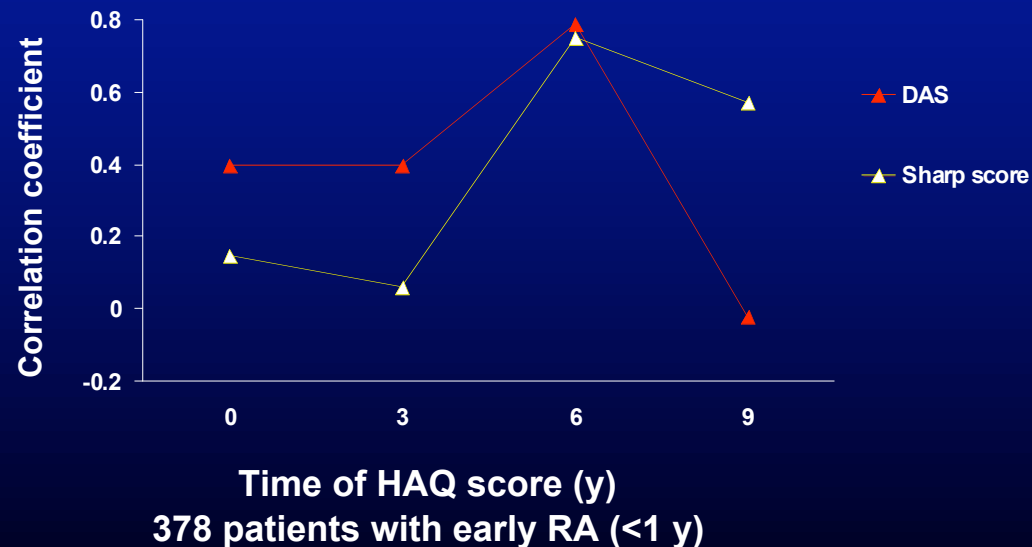
Disease duration	<1 y	1-2 y	2-5 y	5-10 y	>10 y
ACR-20 response rates*	53%	43%	44%	38%	35%

- Uniform decline in ACR response with greater disease duration
- Multivariate analysis showed disease duration had the strongest impact on patient response to treatment (odds ratio=0.97 to 0.98 per year)

*ACR response rates in patients receiving active treatment.
Anderson JJ, et al. *Arthritis Rheum.* 2000;43:22-29.

Review of Early RA: Correlation Between Disability and Radiographs

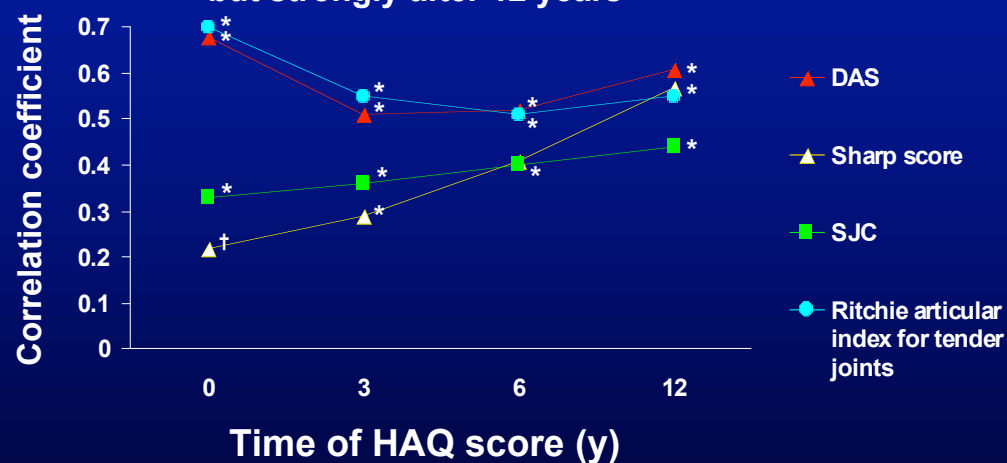
- Correlations between the HAQ and DAS were significant at 0, 3, and 6 years but not at 9 years
- Correlations between the HAQ and Sharp score were significant and higher at 6 and 9 years than at zero and 3 years



Welsing PM, et al. *Arthritis Rheum.* 2001;44:2012.

Review of Early RA: Correlation Between Disability and Radiographs

- DAS correlated strongly with HAQ throughout disease duration
- Sharp score correlated weakly with HAQ at study start but strongly after 12 years



132 women (aged 20-50 years) with early RA

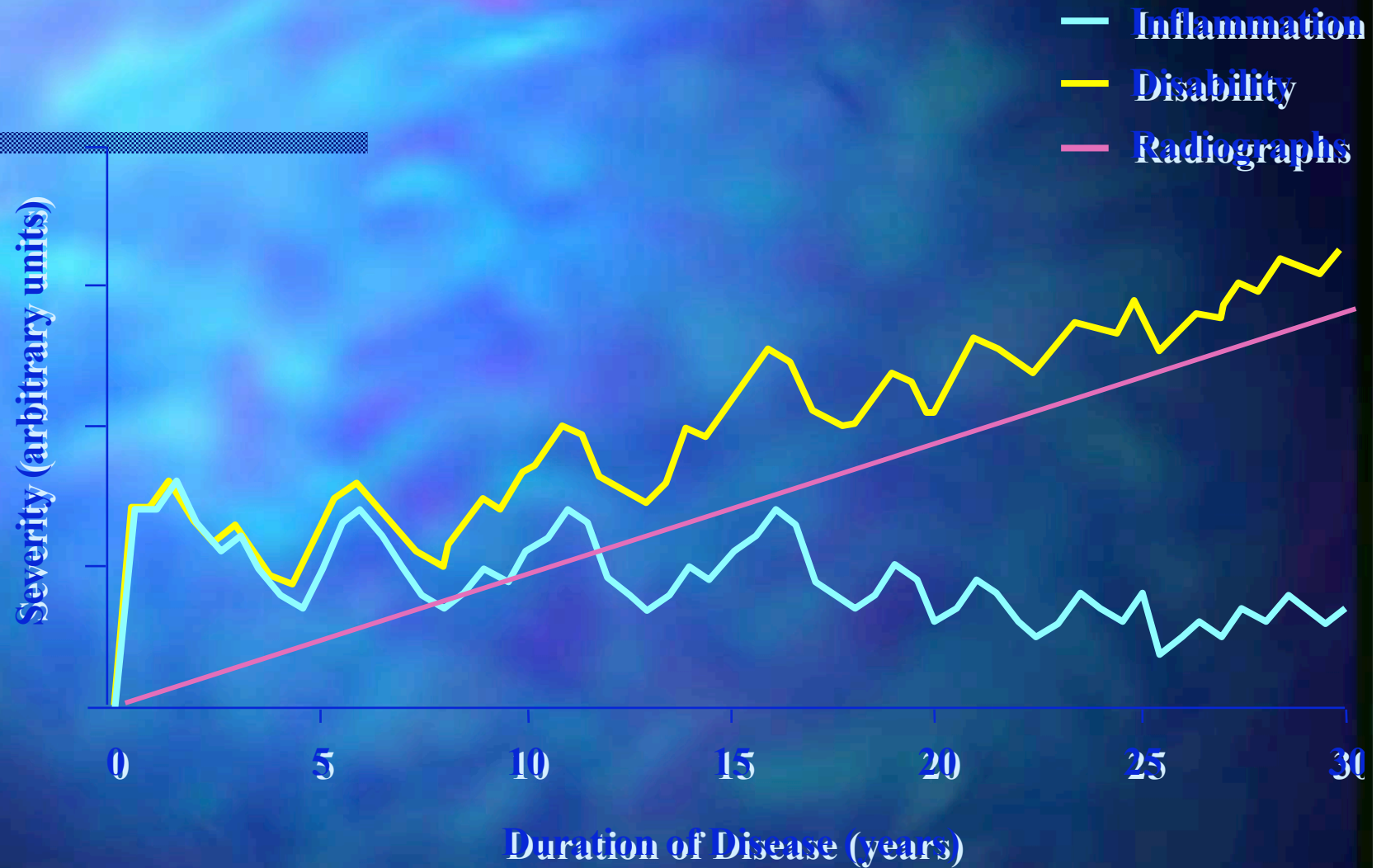
DAS=disease activity score.

* $P < 0.001$.

† $P < 0.05$.

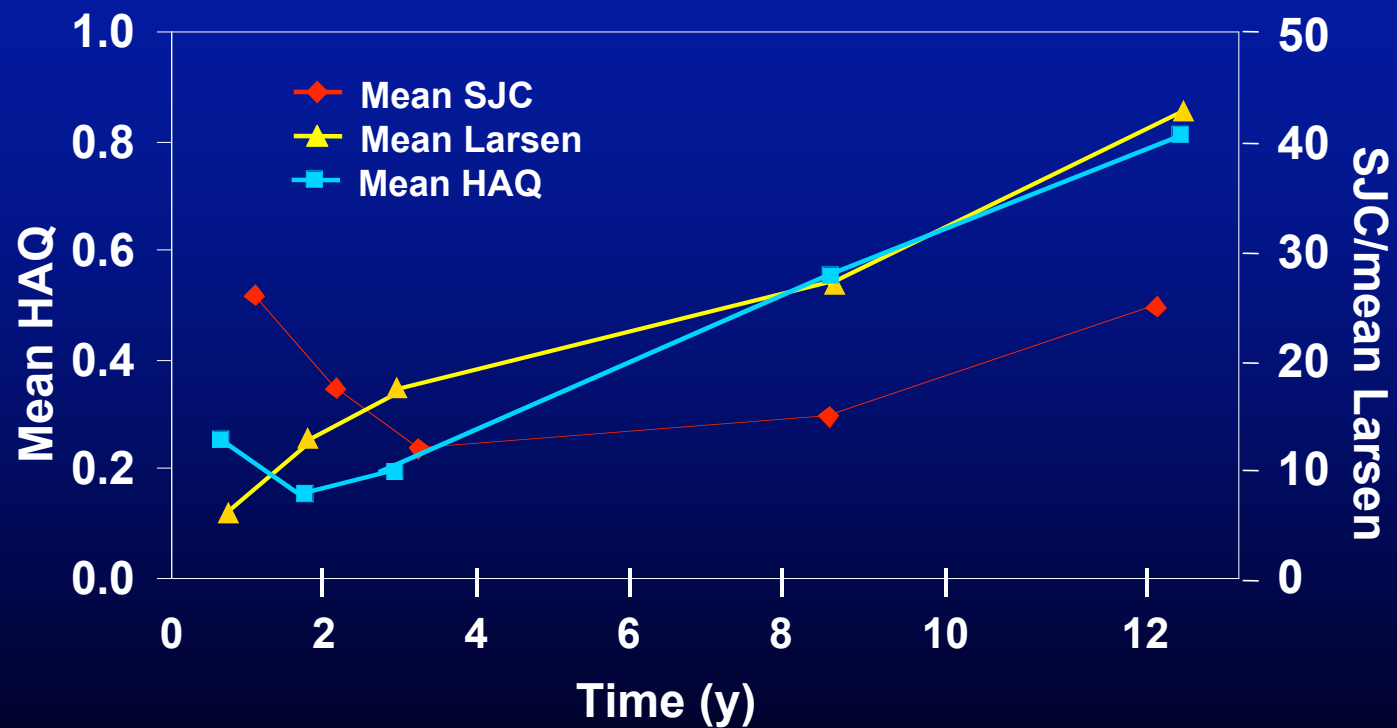
Drossaers-Bakker KW, et al. *Arthritis Rheum.* 1999;42:1854-1860.

RA Progression



Adapted from Kirwan JR. *J Rheumatol.* 2001;23:331-336.

Structural Damage and Disability Progresses Even Though Signs (SJC) Improve



Leirisalo-Repo M, et al. Presented at: ACR 63rd Annual Scientific Meeting; November 1999; Boston, Mass.

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Is there a way to predict a bad outcome in RA

- Not entirely, although presence of RF, high initial disease activity, physical disability, HLA-DR4 and radiographic damage at presentation.
- However, early treatment may negate some of these negative features.
- Most rheumatologists now feel that early treatment with a DMARD is warranted early, rather than late.

Newer drugs for RA

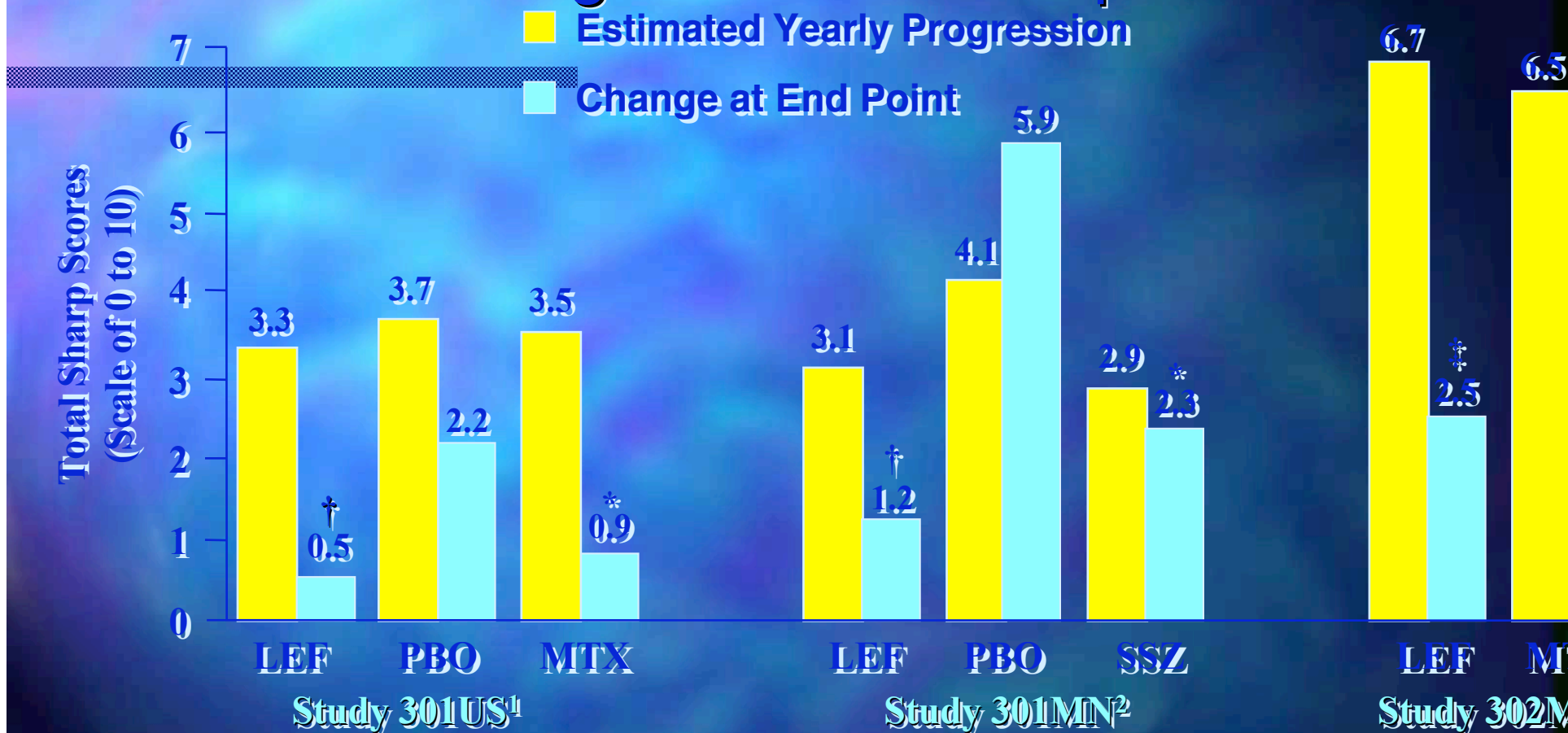
- Infliximab (Remicaide) - chimeric monoclonal Ab
- Etanercept (Enbrel) - soluble receptor
- Adalimumab (Humira) - monoclonal Ab to TNF
- Anakinera (Kineret) - IL 1 receptor antagonist
- Leflunimide (Arava) - a pyrimidine antagonist



How do the old drugs
perform?

Phase III Trials With Traditional DMARD

Changes in Total Sharp Scores



*Active vs PL: ≤ 0.05 ; [†]LEF vs PL: ≤ 0.01 ; [‡]LEF vs MTX: = NS

LEF = leflunomide; MTX = methotrexate; PBO = placebo; SSZ = sulfasalazine

1. Strand V, et al. *Arch Intern Med.* 1999;159:2542–2550; 2. Smolen JS, et al. *Lancet.* 1999;353:259–266;

3. Emery P, et al. *Rheumatology.* 2000;39:655–665.

ACR Response Rates: Traditional DMARDs

% Responders at 12 Months

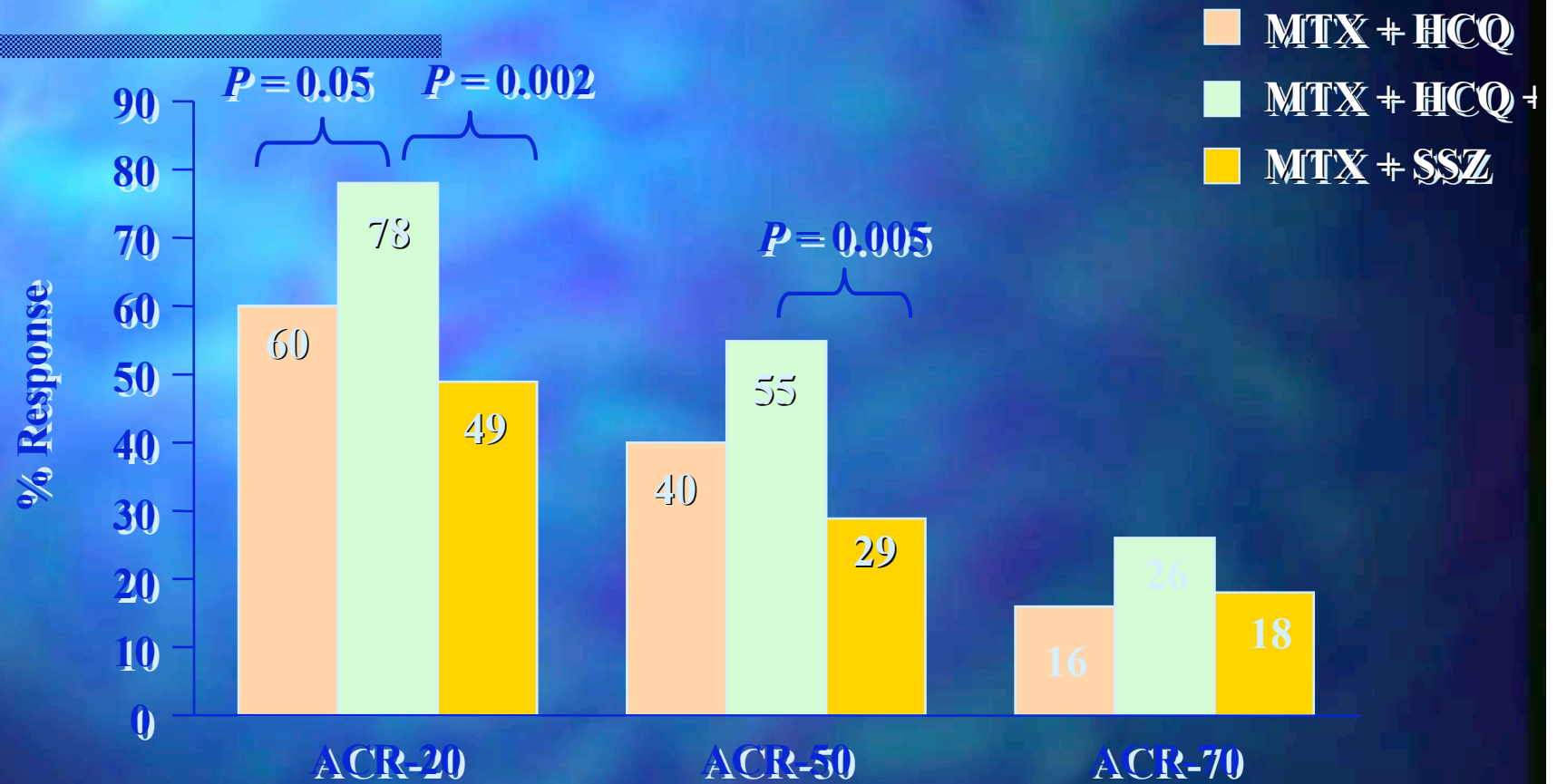
	PBO (n = 118)	LEF (n = 182)	MTX (n = 182)
ACR-20	26	52*	46*
ACR-50	8	34*	23*
ACR-70	4	20*	9

LEF = leflunomide; MTX = methotrexate; PBO = placebo

* $P \leq 0.001$ vs placebo

Strand V, et al. *Arch Intern Med.* 1999;159:2542–2550.

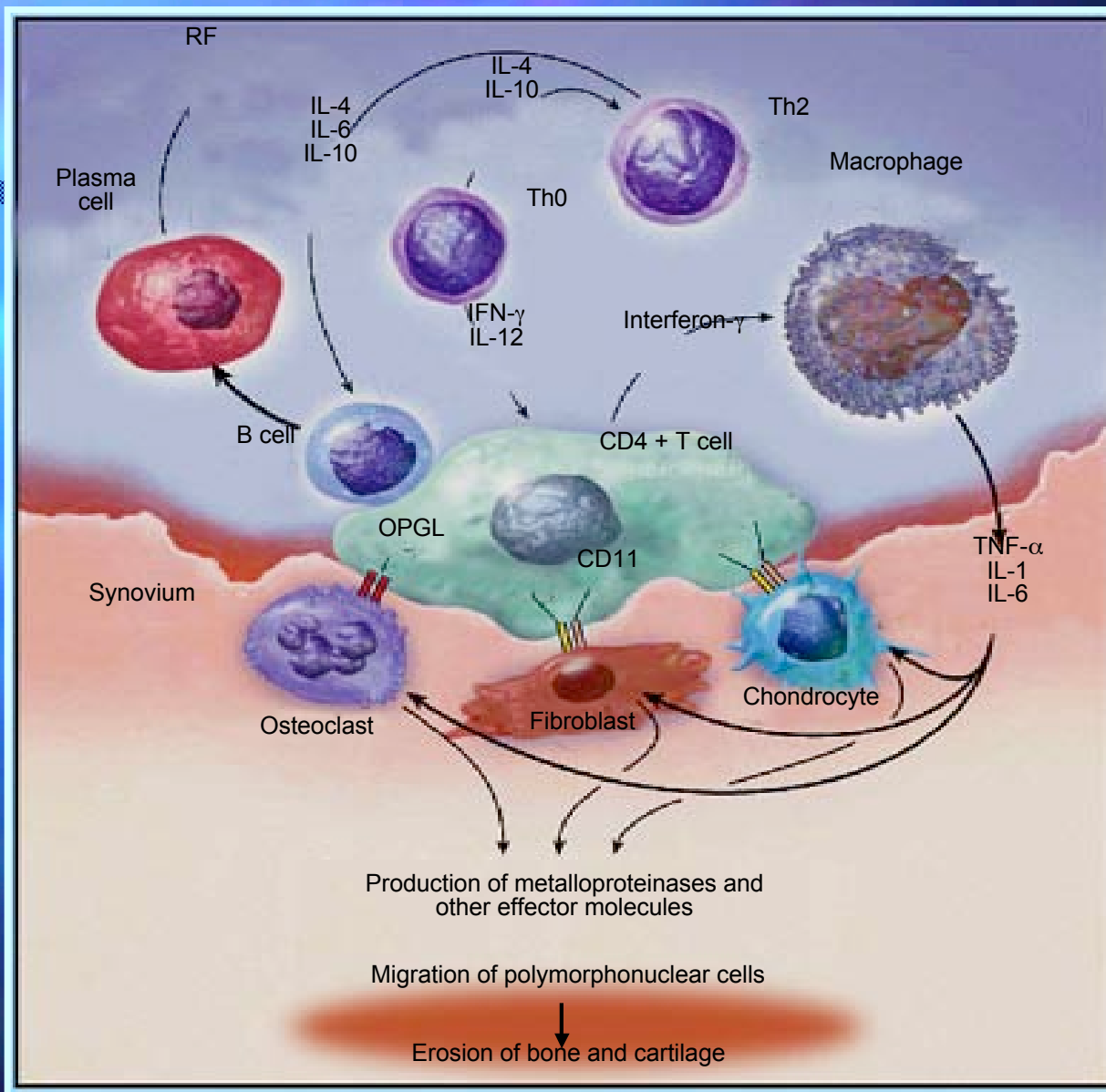
Efficacy of Triple Therapy in RA



TNF inhibitors

- Very effective - have revolutionized treatment of this disease. Remarkably rapid response rates in early and late diseases.

The evidence that TNF is central to RA



TNF- α Inhibitors

Anti-TNF- α mAbs

- **Infliximab**
 - Chimeric (human/murine) IgG1 monoclonal antibody
 - Binds to soluble, transmembrane-bound, and receptor-bound forms of TNF- α
 - Does not bind TNF- β (LT- α)
 - Lyses cells expressing TNF- α
- **Adalimumab**
 - Fully human IgG1 monoclonal antibody
 - Binds to soluble, transmembrane-bound, and receptor-bound forms of TNF- α
 - Binds to TNF- α
 - Does not bind LT- α
 - Lyses cells expressing TNF- α

Fusion Protein

- **Etanercept**
 - Dimeric soluble form of the p75 TNF receptor
 - Binds to TNF- α and LT- α
 - Does not lyse cells expressing TNF- α

LT- α =lymphotoxin- α

Remicade [package insert]. Malvern, Pa: Centocor, Inc; 2002.

Enbrel [package insert]. Thousands Oaks, Calif: Wyeth and Amgen Inc; 2002.

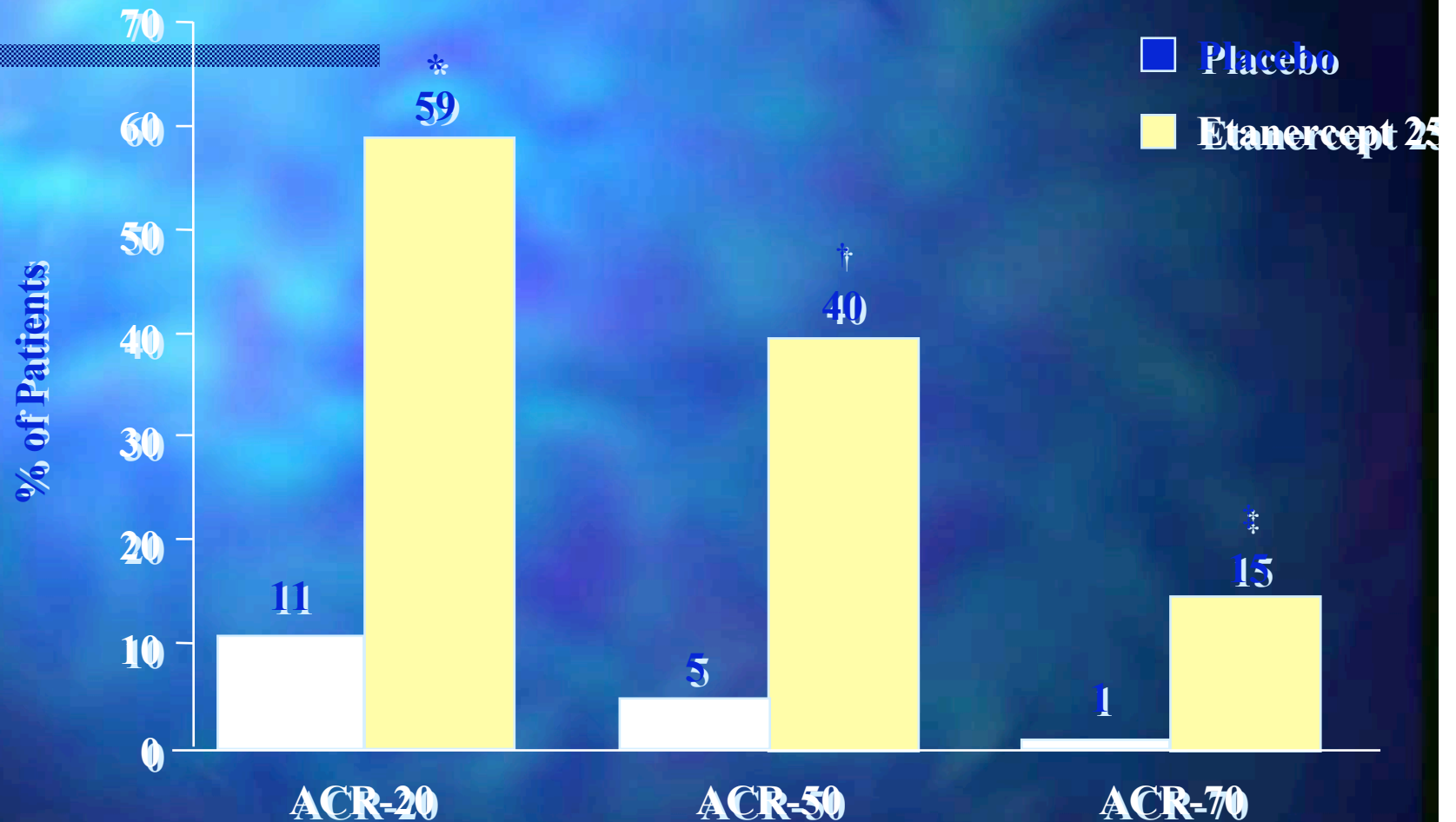
Humira [package insert]. Abbott Park, Ill: Abbott Laboratories; 2002.

The ACR Criteria

- Improvement is denoted as ACR-20, ACR-50, or ACR-70, reflecting an improvement to the 20%, 50%, or 70% level of tender joint counts (TJCs) and swollen joint counts (SJC) plus improvement in 3 of the following:
 - Patient assessment of disease activity
 - Physician assessment of disease activity
 - ESR
 - Pain scale
 - Functional questionnaire
- “The ACR success criteria (20, 50, 70) require that the patient complete the trial and the patient meet ACR responder at the end of the trial”

Johns Hopkins Arthritis Education Guideline. Available at: http://www.hopkins-arthritis.som.jhmi.edu/edu/acr/acr.html#class_rheum. Accessed August 2003.

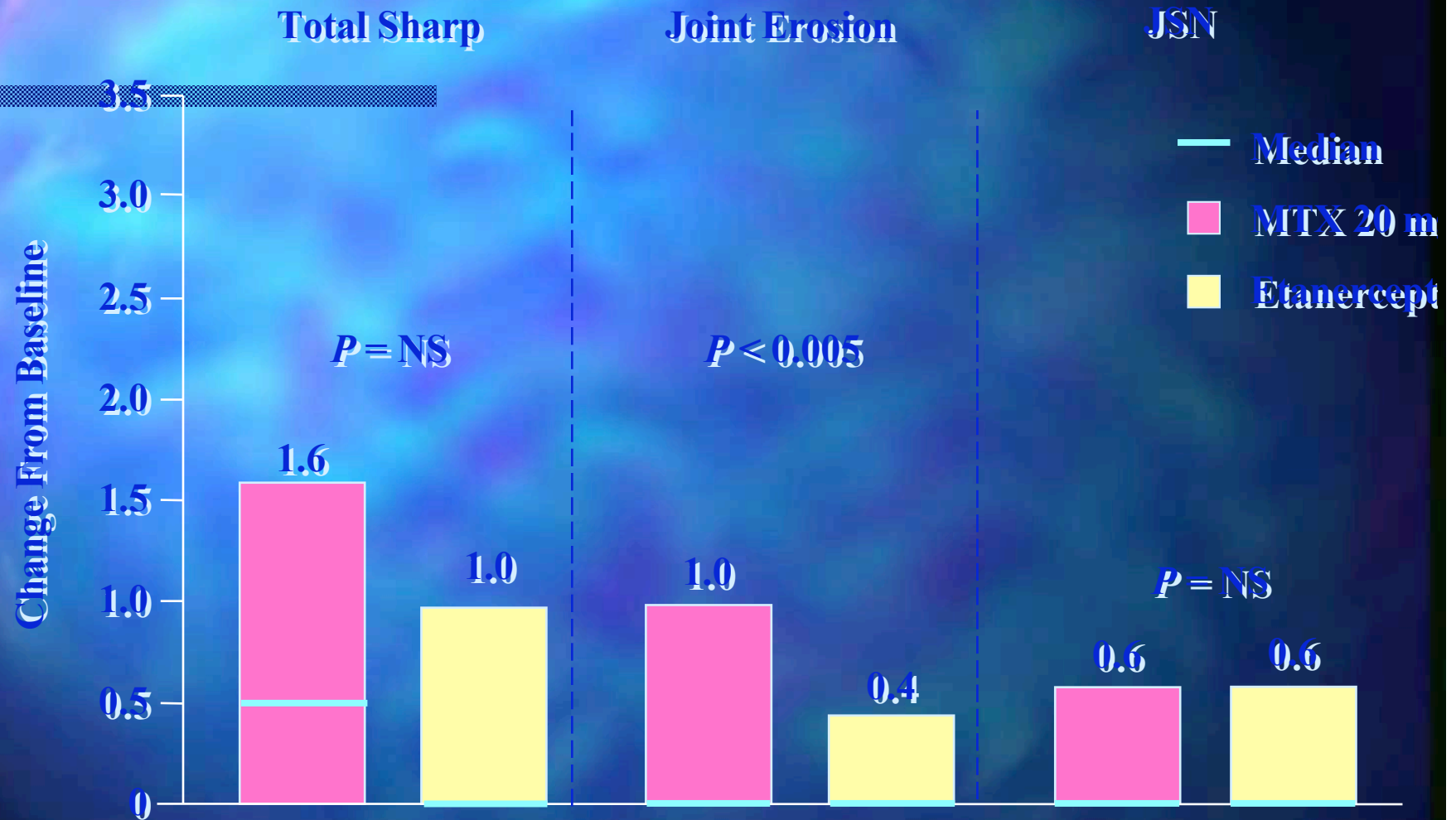
Etanercept Monotherapy: ACR Response Rates at 24 Weeks



* $P < 0.001$; † $P < 0.01$; ‡ $P < 0.05$

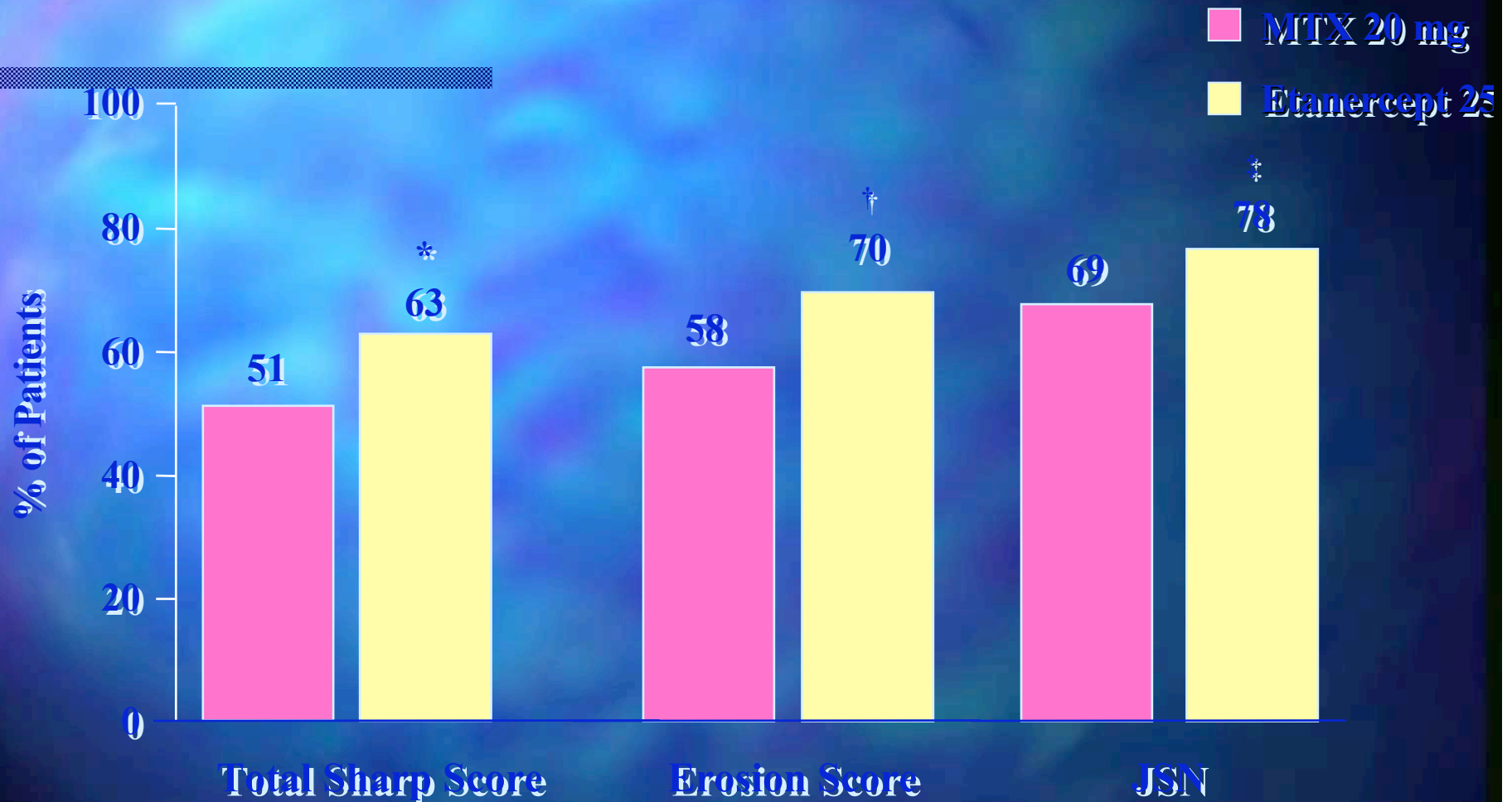
Moreland LW, et al. *Ann Intern Med.* 1999;130:473-486.

Etanercept: Change in Sharp Score 1 Year



Bathon JM, et al. *N Engl J Med*. 2000;343:1536–1593.

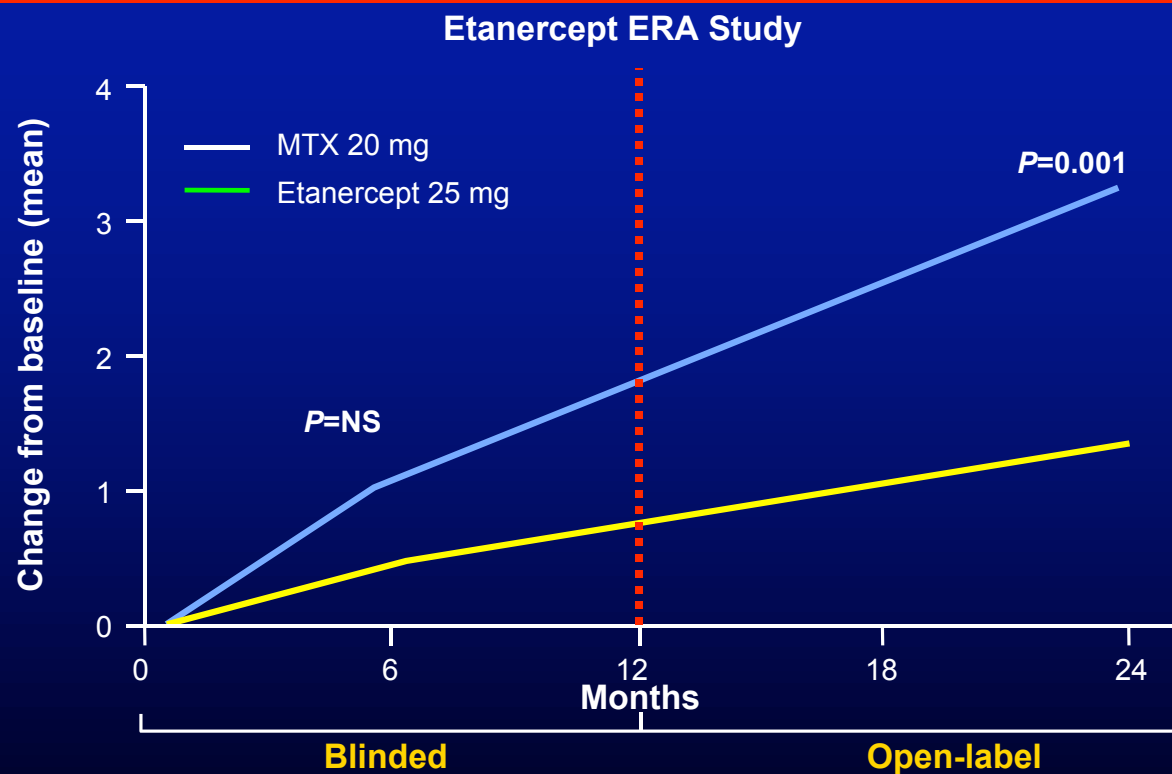
Etanercept in Early RA: Patients With No Radiographic Progression Over 2 Yea



* $P = 0.02$; † $P = 0.01$; ‡ $P = NS$

Genovese MC, et al. *Arthritis Rheum.* 2002;46:1443–1450.

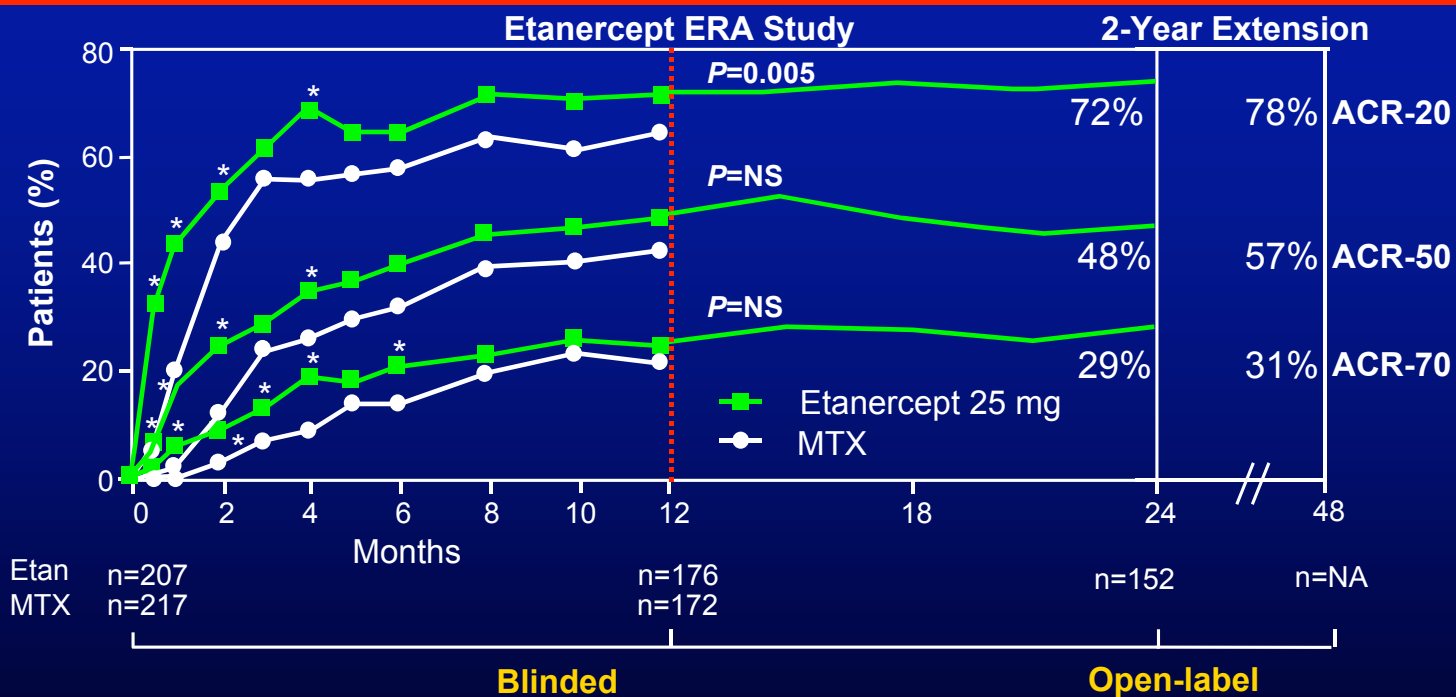
ERA: Change in Total Sharp Scores Through 2 Years



Bathon JM, et al. *N Engl J Med.* 2000;343:1586-1593.

Genovese MC, et al. *Arthritis Rheum.* 2002;46:1443-1450.

ERA: ACR Responses Through 12, 24, and 48 Months



* $P<0.05$.

Bathon JM, et al. *N Engl J Med*. 2000;343:1586-1593.

Genovese MC, et al. *Arthritis Rheum*. 2002;46:1443-1450.

Genovese MC, et al. Presented at: EULAR 2003; June 18-21, 2003; Lisbon, Portugal.

Case two

- A 70yo man comes into your office with complaints of hand pain and deformity. He notes that his symptoms have been present for years with gradual worsening disfigurement. He has come in today because his friend Maude takes Celebrex for her arthritis and is very pleased with the results. He wants to give it a try.

What type of arthritis does he have?

- You can ask more questions....

- He has typical nodal osteoarthritis, a gradually progressing bony enlargement and deformation of the PIP and DIP joints. Pain usually improves with increasing deformity, but disability gets worse. No DMARD exists for this type (or any type) of osteoarthritis.

Who would give him his wish
for celebrex?

Cox 2 selective NSAIDs

- Celecoxib (Celebrex)
- Rofecoxib (Vioxx)
- Valdecoxib (Bextra)
- Meloxicam (Mobic)

Do Cox 2 specific drugs add an advantage?

- Are they better anti-inflammatory drugs?
- Do they carry less cardiovascular effect on blood pressure?
- Do they have less renal adverse effect?
- Do they effect platelets?
- Do they have less gastrointestinal effect?

Evidence for improving GI toxicity from NSAIDs - baseline risk

2-4% per year

- The Cochran reviews conclude that only misoprostel with tradional nonselective Cox inhibitors can decrease both endoscopic and clinically important ulceration.
- However, both celecoxib and rofcoxib have been shown to decrease endoscopic as well as clinically important GI adverse events.
- Celebrex trial (CLASS) JAMA 284:1247-1255; 2000
- Vioxx trial (VIGOR) NEJM 343:1520-1528; 2000
- Cochrane collaboration

The evidence

- VIGOR trial and the CLASS trial
- VIGOR - Vioxx in pts with RA over age 40-50.
- CLASS - Celebrex in OA and RA age >18.
- Outcomes - clinically relevant GI events
- bleeds, perforation, obstruction, ulcer.

The data

- **VIGOR** - >8000 pts with RA randomized to Naprosyn(1000mg) vs Vioxx (50mg). 9 mon F/U. Annualized incidence rates of 2.1 vs 4.5 for a RR of 0.5 in favor of viox. 178 events vs 414.
- **CLASS** - >8000 pts with OA and RA over 18yo randomized to celecoxib (800mg) vs diclofenac (150mg) or ibuprofen (2400mg) for up to 6 mon. Annualized incident rates 1.4% vs 2.91% for a RR reduction of 0.59. 32 vs 51 (26% RA; 25% ASA)
- ***In pts on ASA with Celebrex the rate was 4.70% vs 6.00% p=.49***

The catch....

- Increase in rate of MI especially within 3 months of starting the drug - shown only with Vioxx (and still controversial)
- and....
- Addition of ASA in appropriate pts may negate this effect, but ASA reduces the benefit of the selective Cox 2 inhibition.

Furthermore

- In a study of cost effectiveness using the VIGOR and CLASS data, the average risk pt would need to be 76 for rofecoxib and 81 for celecoxib to be cost effective at the Can\$50,000/QALY
- For pts with prior gastric event (not dyspepsia) both agents are cost effective when compared to NSAIDS with a ppi.

- Maetzel A The cost effectiveness of rofecoxib and celecoxib in patients with osteoarthritis or rheumatoid arthritis Arth Care and Research 49:283-292; 2003

Conclusions

- Diagnosis of RA is a clinical diagnosis first, labs second
- Treatment of early RA is beneficial
- Newer selective meds in RA are very effective.
- Treatment with Cox 2 specific drugs may not be better than less expensive non-selective Cox inhibitors in the usual pt.

May I be excused now... my
brain is full.....
