Rheumatoid Arthritis in 21st century
Where are we heading?

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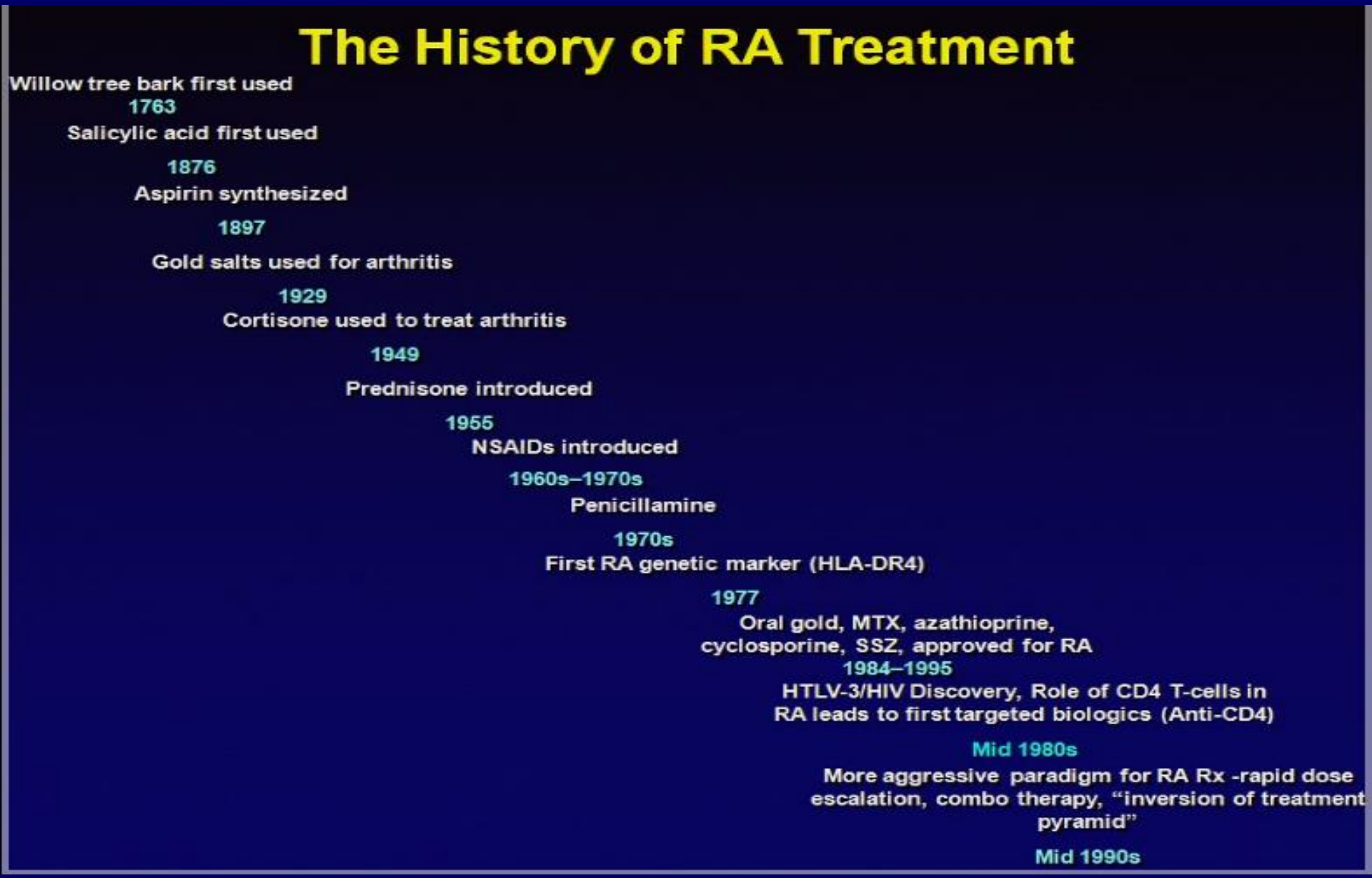
What this talk is about

- How we reached in to the biologic era
- Why is there a need for biologic therapy
- What are the targets of biologic therapy
- Measures of clinical and radiological activity
- Clinical and radiological remission is it “Reality or Fiction”
- What if anti TNF therapy fails
- Looking beyond joints and impact on society
- Weighing risk and benefits of treatment
- Surveillance of co morbidities
- Summary

How we reached in to the biologic era



Into the 21st Century

Leflunomide approved
1998

TNF inhibitors Etanercept and Infliximab approved for RA

1998/1999

COX-2 inhibitors for OA and RA

1999/2000

Anakinra (first IL-1 blocker)

2001

Adalimumab approved
2002

Abatacept approved
2005

Rituximab approved
2006

Golimumab approved
2009

Certolizumab approved
2009

Tocilizumab approved
2010

What this talk is about

- Why is there a need for biologic therapy

Case Study

- Laura came into my office for an urgent appointment more than a year ago. A bright, 25 years old woman, a university student with a bright future . Healthy until recently when suddenly one morning, she could not get out of bed and was unable to dress because her fingers and wrists were swollen, tender, and stiff.

- She had spent some days in bed, then moved back to her parents because she was unable to manage on her own. When I first saw her, she had been ill for about two months, and was just getting worse and worse day-by-day. She had lost 3 kg and was pale, desperate, and tired.

- It was obvious she had rheumatoid arthritis (RA). Tender synovitis in several joints of the hands. She was rheumatoid factor positive, had elevated C-reactive protein and slight anemia. Erosions appeared on her initial ultrasound exam.

- Without delay, she was started on prednisone and methotrexate (MTX) 7.5 mg per week. Two weeks later, when I saw her in the clinic, she was smiling and had returned to the university. She got an injection in a swollen finger joint and I increased the dosage of MTX to 15mg. I assured her she can get appointment within 2 days in case of any swollen joints needs to be injected.

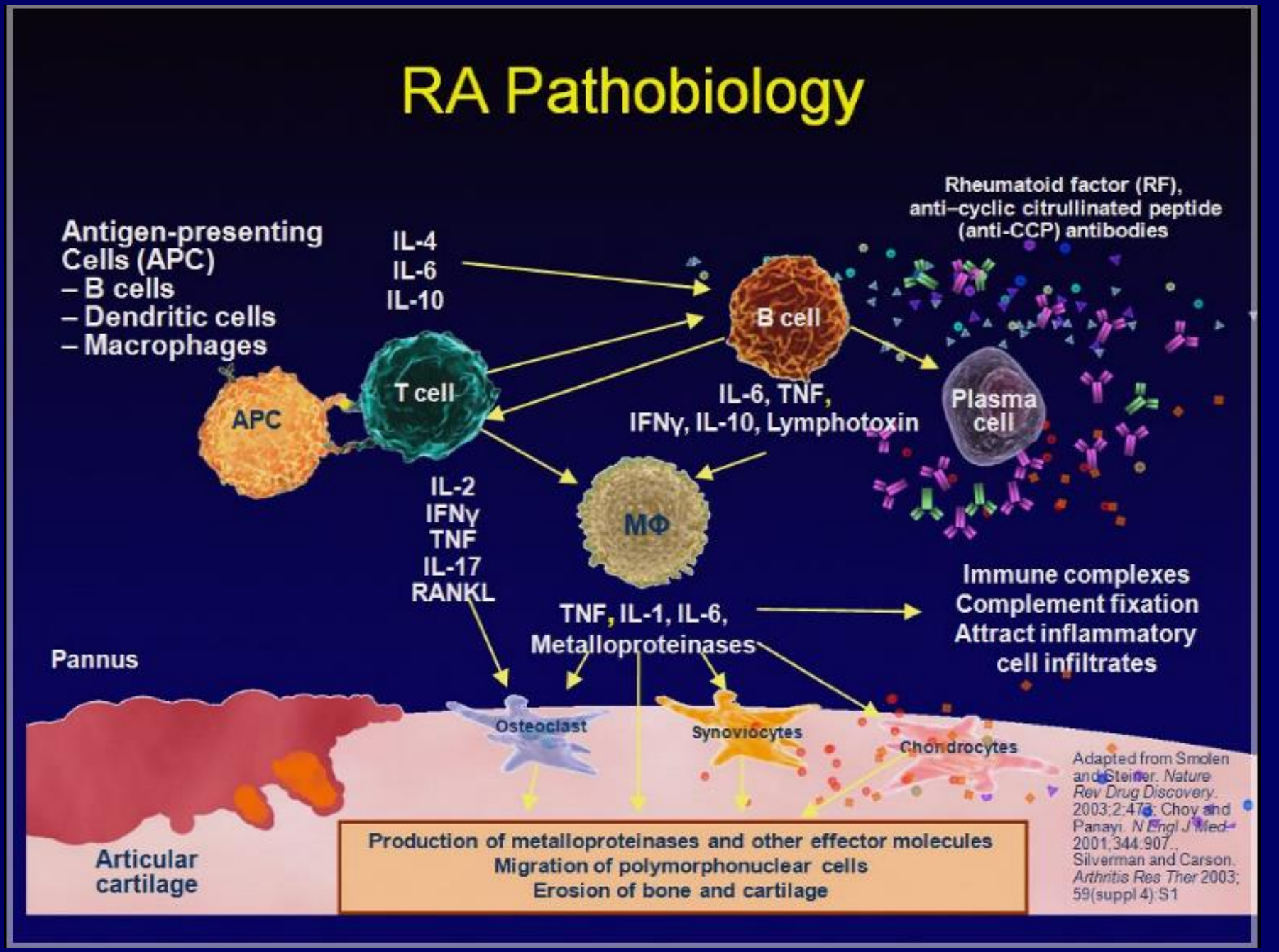
- Six months later she had graduated from university but her condition became worse. She was facing sick leave in her new job. She was she was started on Etanercept in combination with MTX. It worked. She went into remission again.

- For the whole year, there is no progression of joint damage but recently her disease flared again. Many joints are affected causing severe problems in her daily life. She is switched to infliximab (Remicade) which is efficacious for now but what if arthritis showed its ugly face again.

What this talk is about

- What are the targets of biologic therapy

RA Pathobiology



What this talk is about

- Measures of clinical and radiological activity

Review

Improving the Routine Management of Rheumatoid Arthritis: The Value of Tight Control

PHILIP J. MEASE

Table 1. Elements of the Simplified Disease Activity Index (SDAI), the Clinical Disease Activity Index (CDAI), the Disease Activity Score (DAS), and the 28-joint DAS (DAS28)*[24].

Elements	SDAI	CDAI	DAS	DAS28
No. of swollen joints	Simple count (0–28)	Simple count (0–28)	More extensive joint counts (0–2.86)	Simple count, square root transformed (0–1.48)
No. of tender joints	Simple count (0–28)	Simple count (0–28)	Ritchie Index: graded joint counts; square root transformed (0–4.77)	Simple count, square root transformed (0–2.96)
Acute-phase reactants	CRP, mg/dl (0.1–10.0)	–	ESR, log transformed (0.23–1.51)**	ESR, log transformed (0.49–3.22)**
Patient global health	–	–	VAS, mm (0–0.72)**	VAS, mm (0–1.40)**
Patient global disease activity	VAS, cm (0–10.0)	VAS, cm (0–10.0)	–	–
Evaluator global disease activity	VAS, cm (0–10.0)	VAS, cm (0–10.0)	–	–
Total index	No immediate scoring due to CRP; simple calculation possible (0.1–86.0)	Immediate scoring due to CRP; simple calculation possible (0.1–76.0)	No immediate scoring due to ESR; simple calculator required (0.23–9.87)	No immediate scoring due to ESR; simple calculator required (0.49–9.07)

MDHAQ (RAPID-3) questionnaire

RAPID3 Multidimensional Health Assessment Questionnaire (MDHAQ)

YOUR NAME:_____ **Date of Birth:**_____ **Today's date:**_____

1. Please check (☒) the ONE best answer for your abilities at this time:

OVER THE PAST WEEK, were you able to:	Without **ANY** difficulty	With **SOME** difficulty	With **MUCH** difficulty	**UNABLE** to do
Dress yourself, including tying shoelaces, doing buttons?	☐ 0	☐ 1	☐ 2	☐ 3
Get in and out of bed?	☐ 0	☐ 1	☐ 2	☐ 3
Lift a full cup or glass to your mouth?	☐ 0	☐ 1	☐ 2	☐ 3
Walk outdoors on flat ground?	☐ 0	☐ 1	☐ 2	☐ 3
Wash and dry your entire body?	☐ 0	☐ 1	☐ 2	☐ 3
Bend down and pick up clothing from the floor?	☐ 0	☐ 1	☐ 2	☐ 3
Turn regular faucets on and off?	☐ 0	☐ 1	☐ 2	☐ 3
Get in and out of a car, bus, train, or airplane?	☐ 0	☐ 1	☐ 2	☐ 3
Walk two miles?	☐ 0	☐ 1	☐ 2	☐ 3
Participate in sports and games as you would like?	☐ 0	☐ 1	☐ 2	☐ 3

2. How much pain have you had because of your condition **OVER THE PAST WEEK**? Please indicate below how severe your pain has been:

NO PAIN ○ 0 ○ 0.5 ○ 1 ○ 1.5 ○ 2 ○ 2.5 ○ 3 ○ 3.5 ○ 4 ○ 4.5 ○ 5 ○ 5.5 ○ 6 ○ 6.5 ○ 7 ○ 7.5 ○ 8 ○ 8.5 ○ 9 ○ 9.5 ○ 10 **PAIN AS BAD AS IT COULD BE**

3. Considering all the ways in which illness and health conditions may affect you at this time, please indicate below how you are doing:

VERY WELL ○ 0 ○ 0.5 ○ 1 ○ 1.5 ○ 2 ○ 2.5 ○ 3 ○ 3.5 ○ 4 ○ 4.5 ○ 5 ○ 5.5 ○ 6 ○ 6.5 ○ 7 ○ 7.5 ○ 8 ○ 8.5 ○ 9 ○ 9.5 ○ 10 **VERY POORLY**

FN 0–10 ☐

1=0.3 19=5.3
2=0.7 17=5.7
3=1.0 18=6.0
4=1.3 19=6.3
5=1.7 20=6.7
6=2.0 21=7.0
7=2.3 22=7.3
8=2.7 23=7.7
9=3.0 24=8.0
10=3.3 25=8.3
11=3.7 26=8.7
12=4.0 27=9.0
13=4.3 28=9.3
14=4.7 29=9.7
15=5.0 30=10

PN 0–10 ☐

PTGL 0–10 ☐

RAPID 0–30 ☐

ARTHRITIS & RHEUMATISM
Vol. 44, No. 8, August 2001, pp 1736–1743

Published by Wiley-Liss, Inc.

Prognostic Factors for Radiographic Damage in Early Rheumatoid Arthritis

A Multiparameter Prospective Study

Erythrocyte sedimentation rate (ESR)
C-reactive protein level
IgM and IgA rheumatoid factor positivity Antiperinuclear antibody positivity
Radiologic scores
Duration of morning stiffness
RA-associated HLA–DRB1p04 genes

Genetic predisposition

Table 4. HLA–DRB1 genotype and radiographic progression during 3 years*

	No progression (n = 97)	Progression (n = 70)
DRB1*04/04†	4 (4.1)	8 (11.4)
DRB1*04/01	5 (5.2)	9 (12.9)
DRB1*04/X	29 (29.9)	27 (38.6)
DRB1*01/01	1 (1.0)	2 (2.9)
DRB1*X/X	32 (33.0)	17 (24.3)
DRB1*01/X	26 (26.8)	7 (10.0)

* Values are the no. (%) of patients. $P = 0.013$ between groups, by chi-square test.
† DRB1*04 includes DRB1*0401, 0404, 0405, and 0408.

Table 6. Stepwise logistic regression analysis of predictive factors of high (>4) Sharp score at 3 years*

	Coefficient	SE	OR	95% CI
Constant	−3.074	0.747		
Initial Sharp score	3.438	0.564	31.1	10.2–95.0
IgM RF positivity	1.065	0.583	2.90	0.9–9.2
DRB1*04 positivity†	1.057	0.521	2.88	1.0–8.0
Pain ≥59 mm‡	0.881	0.511	2.41	0.8–6.6

* Initial Sharp score, IgM rheumatoid factor (RF) positivity and DRB1*04 positivity were entered as categorical variables (0 = low or absent; 1 = high or present). Four is the median value of the total Sharp score at 3 years. OR = odds ratio; 95% CI = 95% confidence interval.
† DRB1*04 includes DRB1*0401, 0404, 0405, and 0408.
‡ Median value at baseline (on a visual analog scale of 0–100).

Remember joint damage is progressive

ARTHRITIS & RHEUMATISM
Vol. 43, No. 9, September 2000, pp 1927–1940

THE COURSE OF RADIOLOGIC DAMAGE DURING THE FIRST SIX YEARS OF RHEUMATOID ARTHRITIS

Conclusion. **Radiologic damage progresses at a constant rate. In advanced disease, monitoring the progression of previously existing damage is as important as assessing new abnormalities in previously undamaged joints. Radiographs of the feet should be included in assessments of radiologic damage that are used in clinical intervention trials and daily practice.**

RADIOLOGIC DAMAGE DURING THE FIRST SIX YEARS OF RA

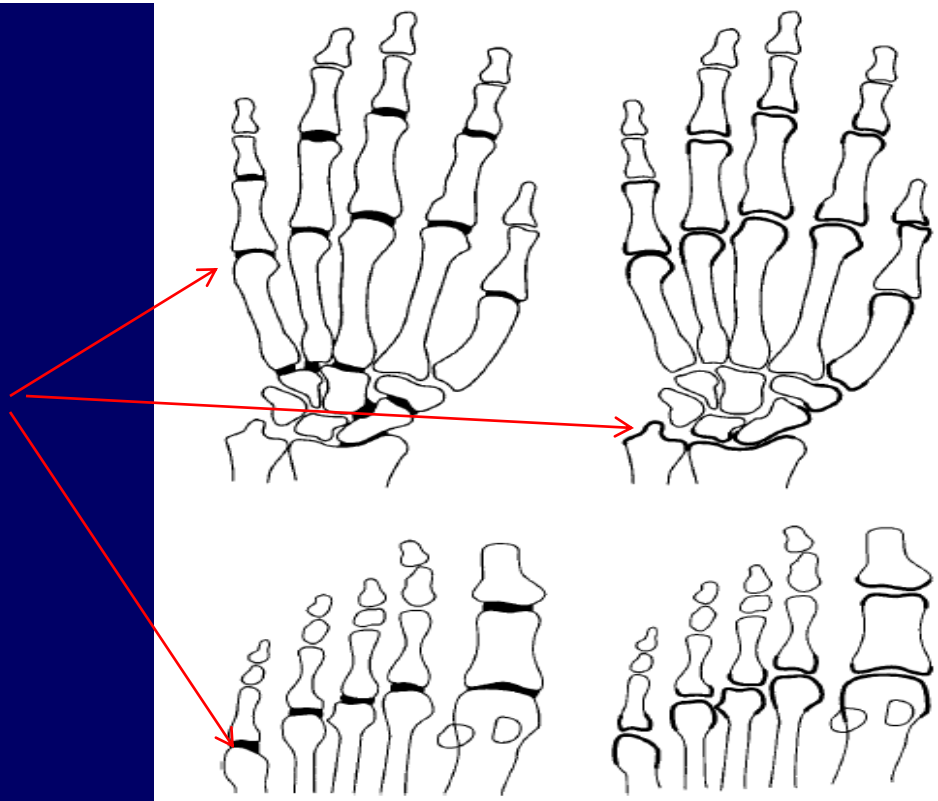


Figure 1. Joints and joint areas **(boldfaced areas)** scored for joint space narrowing **(left)** and erosions **(right)** using the van der Heijde modification of the Sharp scoring method.

Study population and entry criteria. The study population consisted of patients with early RA, according to the American College of Rheumatology (formerly, the American Rheumatism Association) 1987 criteria (32), who had participated in a randomized trial begun in 1990 comparing the effectiveness and toxicity of therapeutic strategies at 6 rheumatology centers in the Utrecht region of The Netherlands. Patients entering the study were randomized to undergo treatment with hydroxychloroquine (400 mg/day), aurothioglucose (50 mg/week), or methotrexate (7.5–15 mg/week).

Progressive Joint Damage

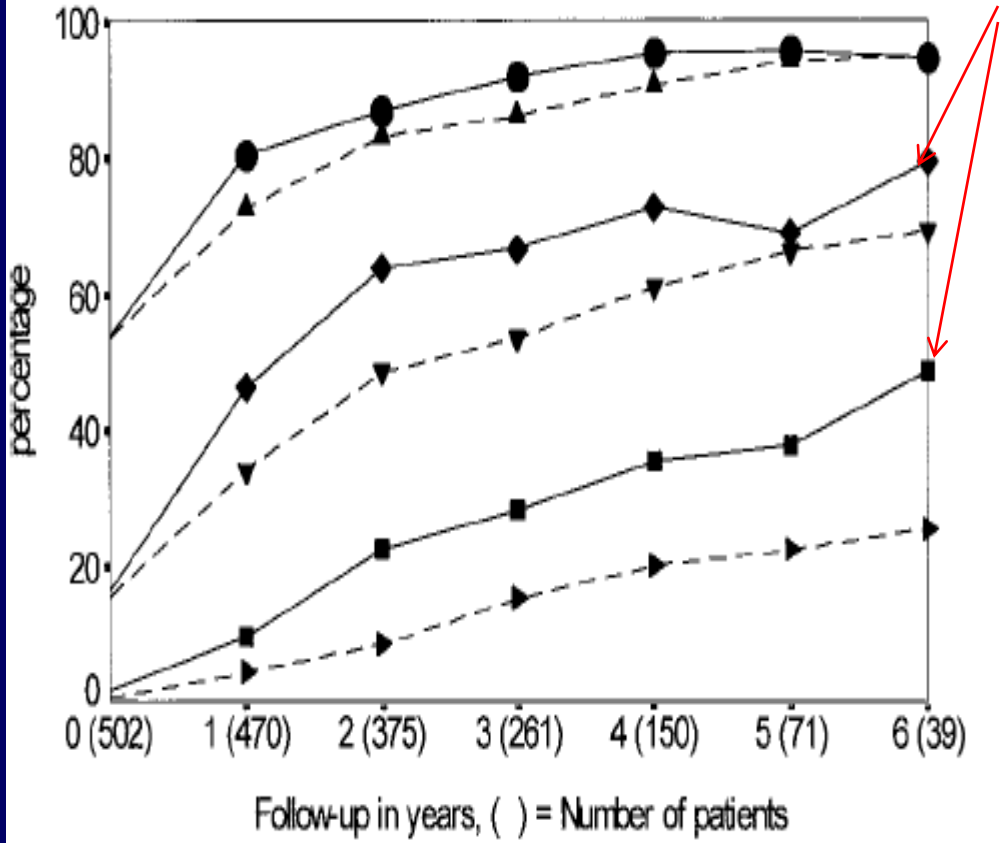


Figure 2. Percentages of patients with erosions (——) and joint space narrowing (– – –) at different cutoff points. Erosion score cutoffs were ≥1 (●), ≥5 (♦), and ≥20 (■); narrowing score cutoffs were ≥1 (▲); ≥5 (▼), and ≥20 (▶).

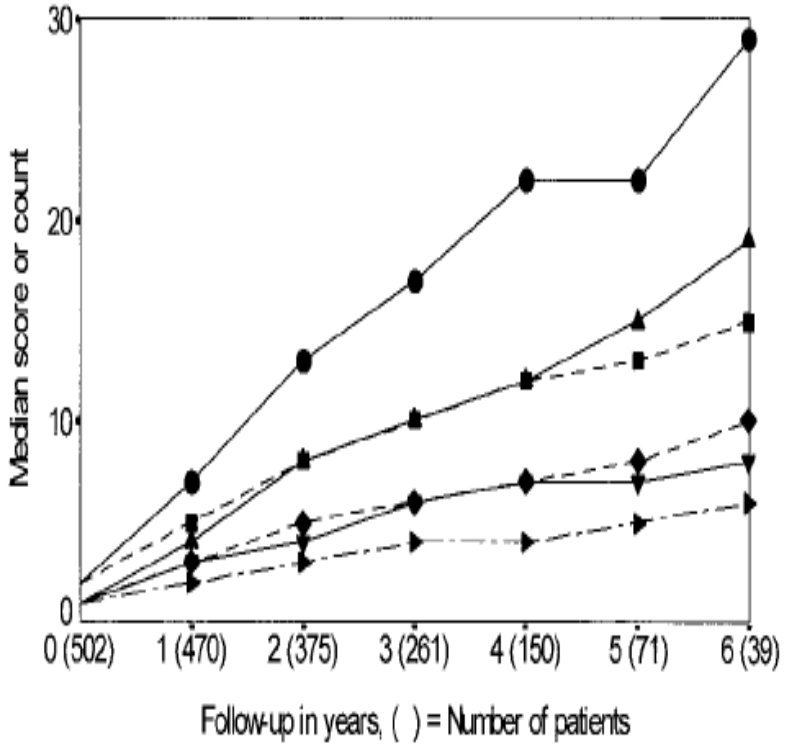


Figure 3. Radiologic progression of rheumatoid arthritis, as indicated by scores (——) and counts (– – –). The median Sharp score as modified by van der Heijde (●), erosion score (▲), and narrowing score (▼) suggest a linear course of development of radiologic abnormalities. Rates of progression of the Sharp count (■), erosion count (♦), and narrowing count (▶) show a tendency toward a decrease over time. See Patients and Methods for details.

Ultrasonograhic assessment

Table 1. Synovial intraarticular recesses and periarticular sites at each joint evaluated by power Doppler ultrasonography

Joints (bilateral)*	Synovial sites
Shoulder	Posterior recess, axillar recess, biceps tendon sheath, subdeltoid bursa
Elbow	Anterior recess, posterior recess
Wrist	Dorsal carpal recesses, volar carpal recesses, extensor tendon sheaths, flexor tendon sheaths
Knee	Suprapatellar recess, medial parapatellar recess, lateral parapatellar recess
MCP and PIP of hands	Dorsal recess, palmar recess, flexor tendon sheaths

* MCP = metacarpophalangeal; PIP = proximal interphalangeal.

ARTHRITIS & RHEUMATISM
Vol. 58, No. 8, August 2008, pp 2248–2256
DOI 10.1002/art.23682

ARTHRITIS & RHEUMATISM
Vol. 52, No. 3, March 2005, pp 733–743
DOI 10.1002/art.20939

A Novel Ultrasonographic Synovitis Scoring System Suitable for Analyzing Finger Joint Inflammation in Rheumatoid Arthritis

Conclusion. **US evaluation of finger joint synovitis can be considerably simplified by focusing on the palmar side and by applying semiquantitative grading instead of quantitative measurements. For evaluation of treatment efficacy based on synovitis in RA patients, we recommend using the "sum of 3 fingers" method in longitudinal trials.**

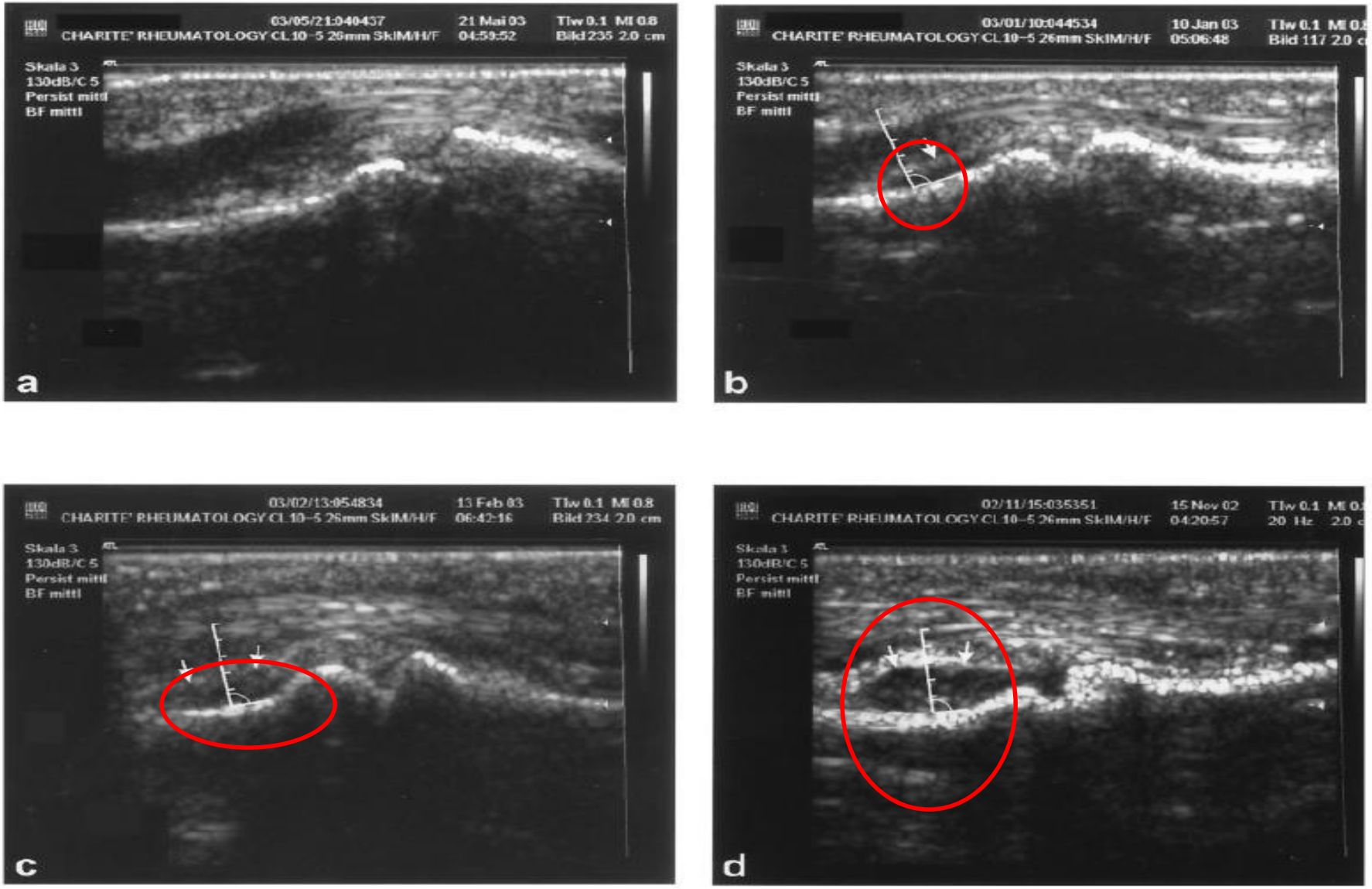


Figure 1. Ultrasound images of the second proximal interphalangeal (PIP) joints of rheumatoid arthritis patients with different stages of synovitis. No erosions are visible in any of the images. Images were taken from the palmar side; the left side of the image is the proximal side of the hand and the right side the distal side. Effusion and synovitis of varying extents can be seen. Inflammation is seen mainly at the palmar proximal side of the PIP joint. All images were graded semiquantitatively with regard to the degree of inflammation, interpreted based on effusion and synovitis, as follows: 0 = none (**a**); 1 = little (**b**); 2 = moderate (**c**); and 3 = high (**d**). Measurements were performed in a standardized manner, at the proximal site perpendicular to the bone surface at the diaphysis at the point where the most synovitis was seen (on scale bars in **b–d,** hatch marks are 0.5 mm apart). **Arrows** indicate the margins of the synovitis.

ARTHRITIS & RHEUMATISM
Vol. 48, No. 7, July 2003, pp 1828–1832
DOI 10.1002/art.11039

Doppler Sonographic Findings in the Long Bicipital Tendon Sheath in Patients With Rheumatoid Arthritis as Compared With Patients With Degenerative Diseases of the Shoulder

Conclusion. **PDS demonstrates vascularity in the long bicipital tendon sheath of patients with RA, but not in those with degenerative shoulder disorders.**

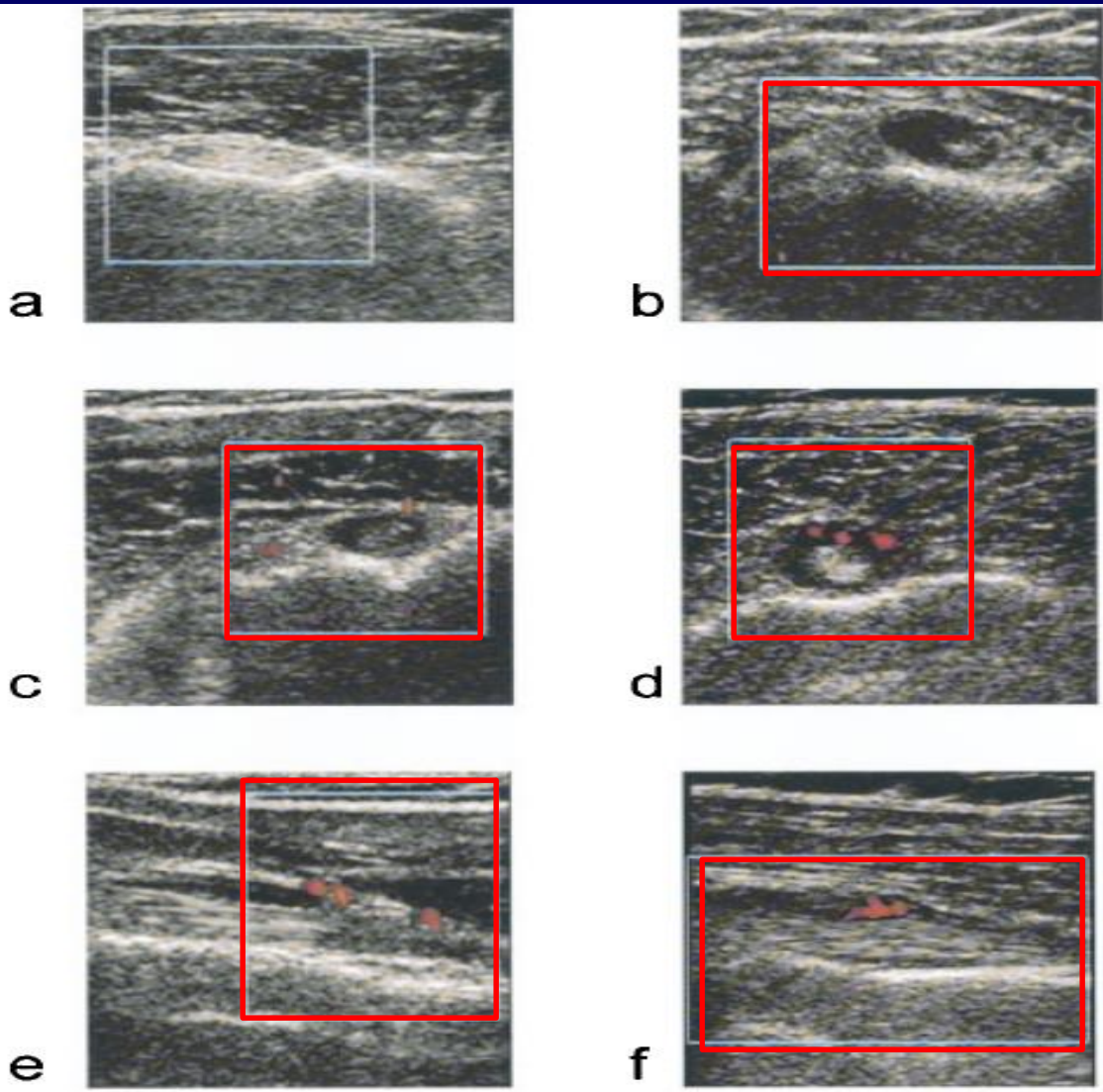


Figure 1. a–d, Ventral transverse and e and f, longitudinal ultrasonographic scans of the shoulder, demonstrating the long bicipital tendon with its tendon sheath. a, Tendon sheath without effusion or power Doppler signal (PDS). b, Tendon sheath with marked effusion, without PDS. c and e, Effusion inside the tendon sheath, and PDS outside. d and f, Effusion and PDS inside the tendon sheath.

ARTHRITIS & RHEUMATISM
Vol. 48, No. 4, April 2003, pp 955–962
DOI 10.1002/art.10877

Interobserver Agreement in Ultrasonography of the Finger and Toe Joints in Rheumatoid Arthritis

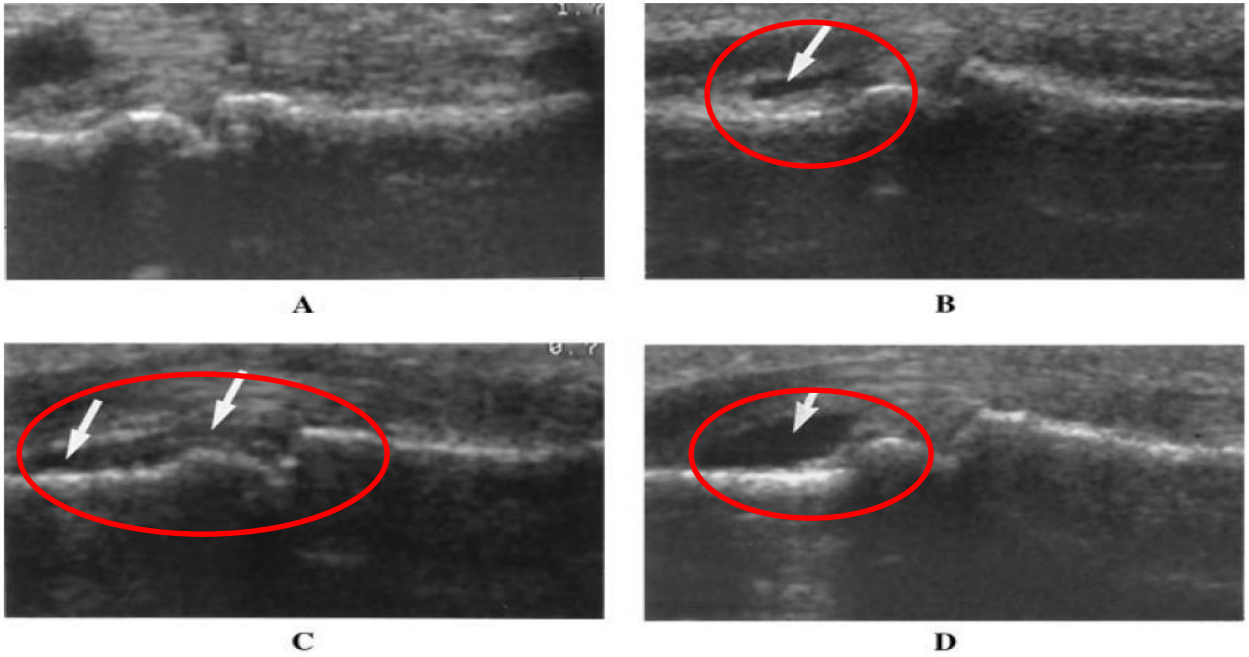


Figure 1. Joint effusion on ultrasonography. **A**, Grade 0 = no fluid; **B**, grade 1 = minimal amount of fluid (**arrow**); **C**, grade 2 = moderate amount of fluid (without distension of the joint capsule) (**arrows**); **D**, grade 3 = extensive amount of fluid (with distension of the joint capsule) (**arrow**).

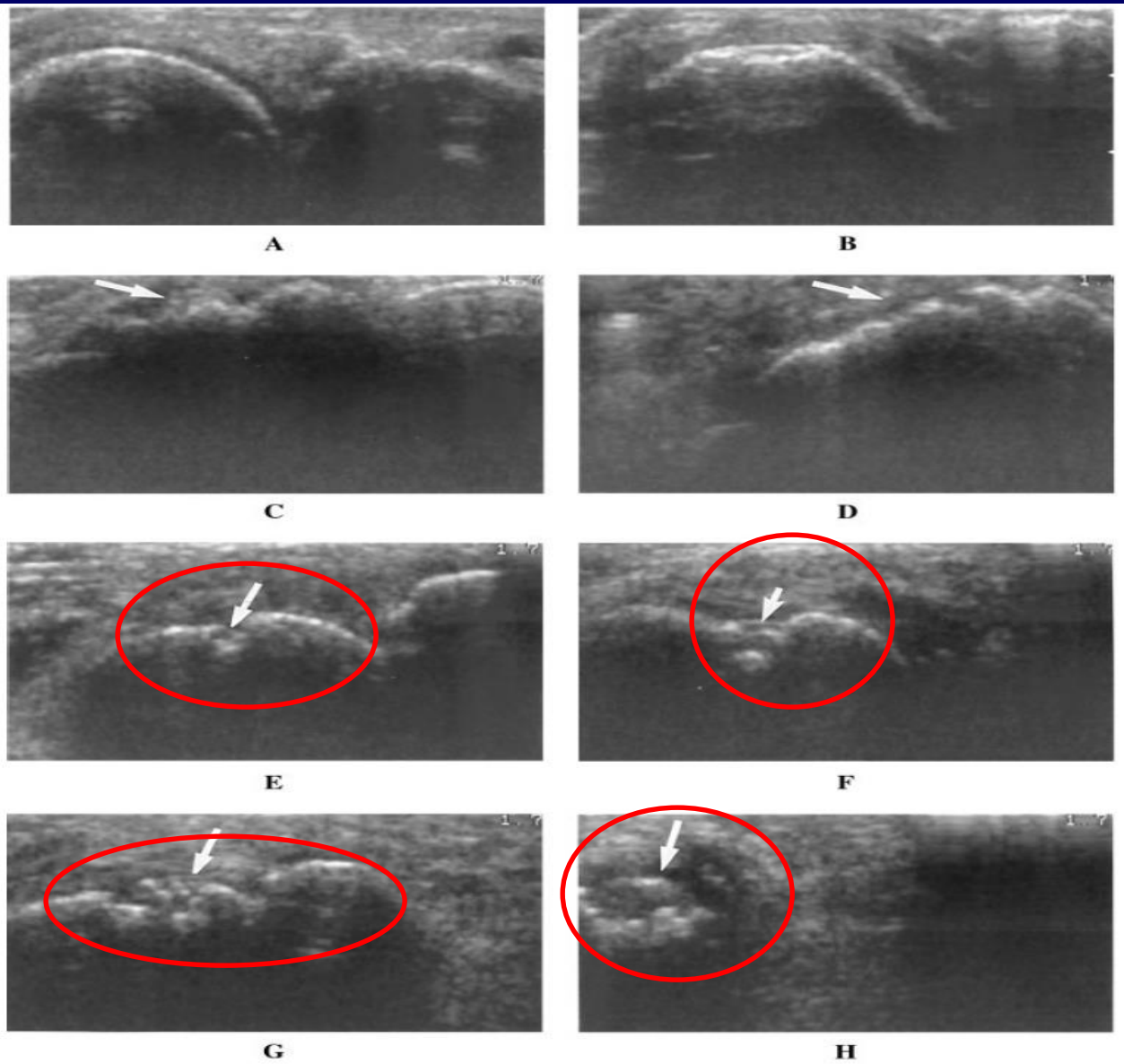


Figure 3. Bone changes scored with ultrasonography, with each joint visualized in 2 planes (longitudinal and transverse). **A** and **B**, Grade 0 = regular bone surface; **C** and **D**, grade 1 = irregularity of the bone surface without formation of a defect seen in 2 planes (**arrow**); **E** and **F**, grade 2 = formation of a defect in the surface of the bone seen in 2 planes (**arrow**); **G** and **H**, grade 3 = bone defect creating extensive bone destruction (**arrow**).

ARTHRITIS & RHEUMATISM
Vol. 48, No. 9, September 2003, pp 2434–2441
DOI 10.1002/art.11245

Doppler Ultrasound and Magnetic Resonance Imaging of Synovial Inflammation of the Hand in Rheumatoid Arthritis

A Comparative Study

Conclusion. **Estimates of synovial inflammatory activity by Doppler US and postcontrast MRI were comparable. Estimation of synovial inflammatory activity by the RI and color fraction parameters of US appears to be a promising method of detecting and monitoring inflammatory activity in patients with RA.**

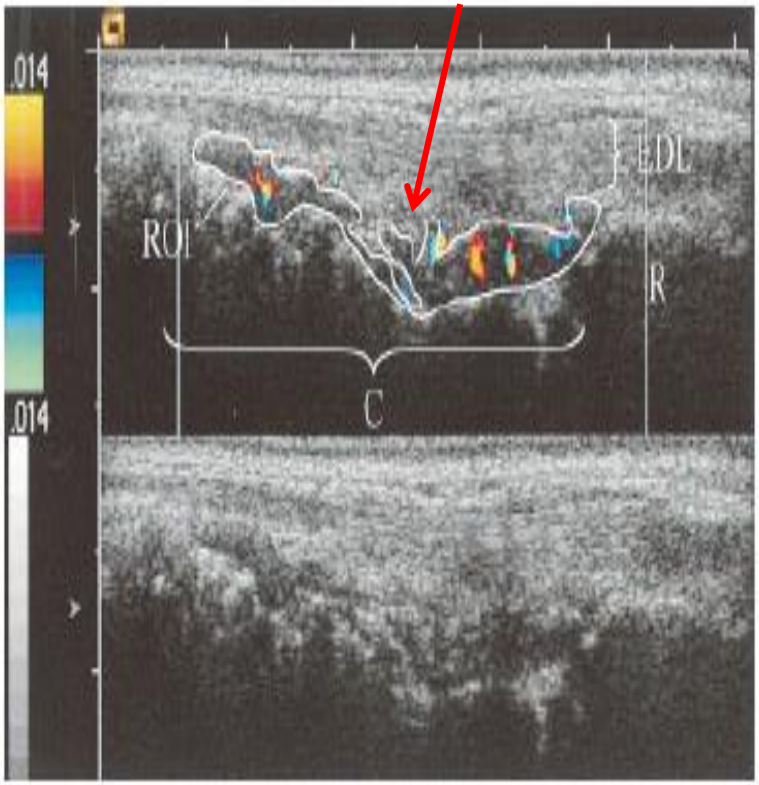


Figure 1. Appearance of inflammation in the wrist on color Doppler ultrasound. Longitudinal scan in the middle of the right wrist. **Top,** Color Doppler activity in the synovium (the region of interest **[ROI]**, which is outlined), covering the eroded carpal bones (**C**), indicating the presence of inflammation. The surface of the radius (**R**) and the extensor digitorum longus (**EDL**) tendon are indicated on the right. **Bottom,** Corresponding gray-scale image from which the color Doppler information has been removed.

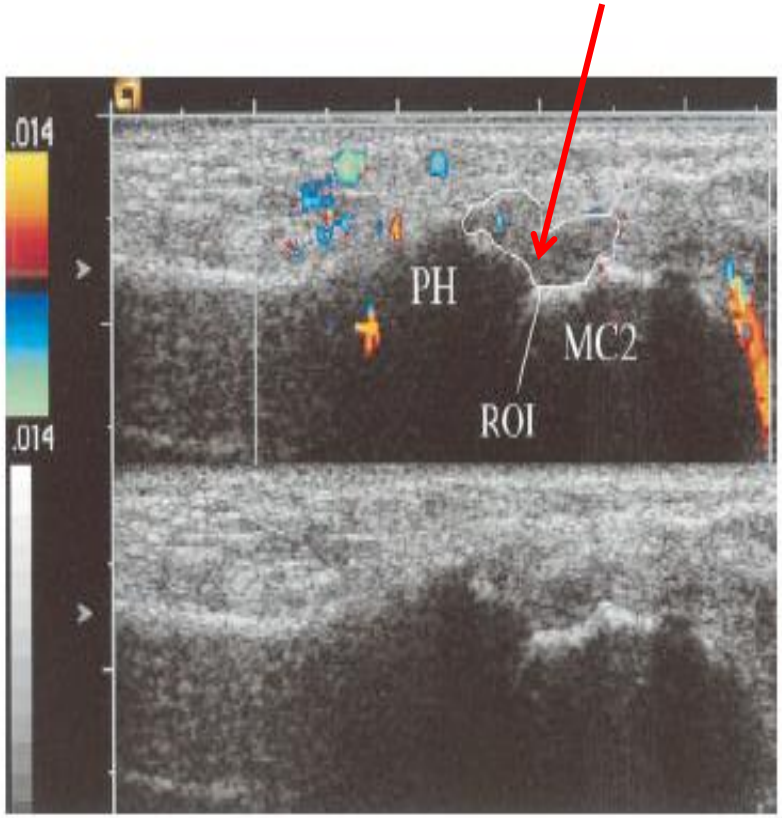


Figure 4. Appearance of inflammation in the metacarpophalangeal (MCP) joint on color Doppler ultrasound. Longitudinal scan in the frontal plane on the radial side of the right second MCP joint. **Top,** Color Doppler activity in the synovium (i.e., the region of interest **[ROI]**, which is outlined). The single minute spot of color indicates the presence of inflammation. The head of the metacarpal bone (**MC2**) and the base of the proximal phalanx (**PH**) are indicated. **Bottom,** Corresponding gray-scale image from which the color Doppler information has been removed.

What this talk is about

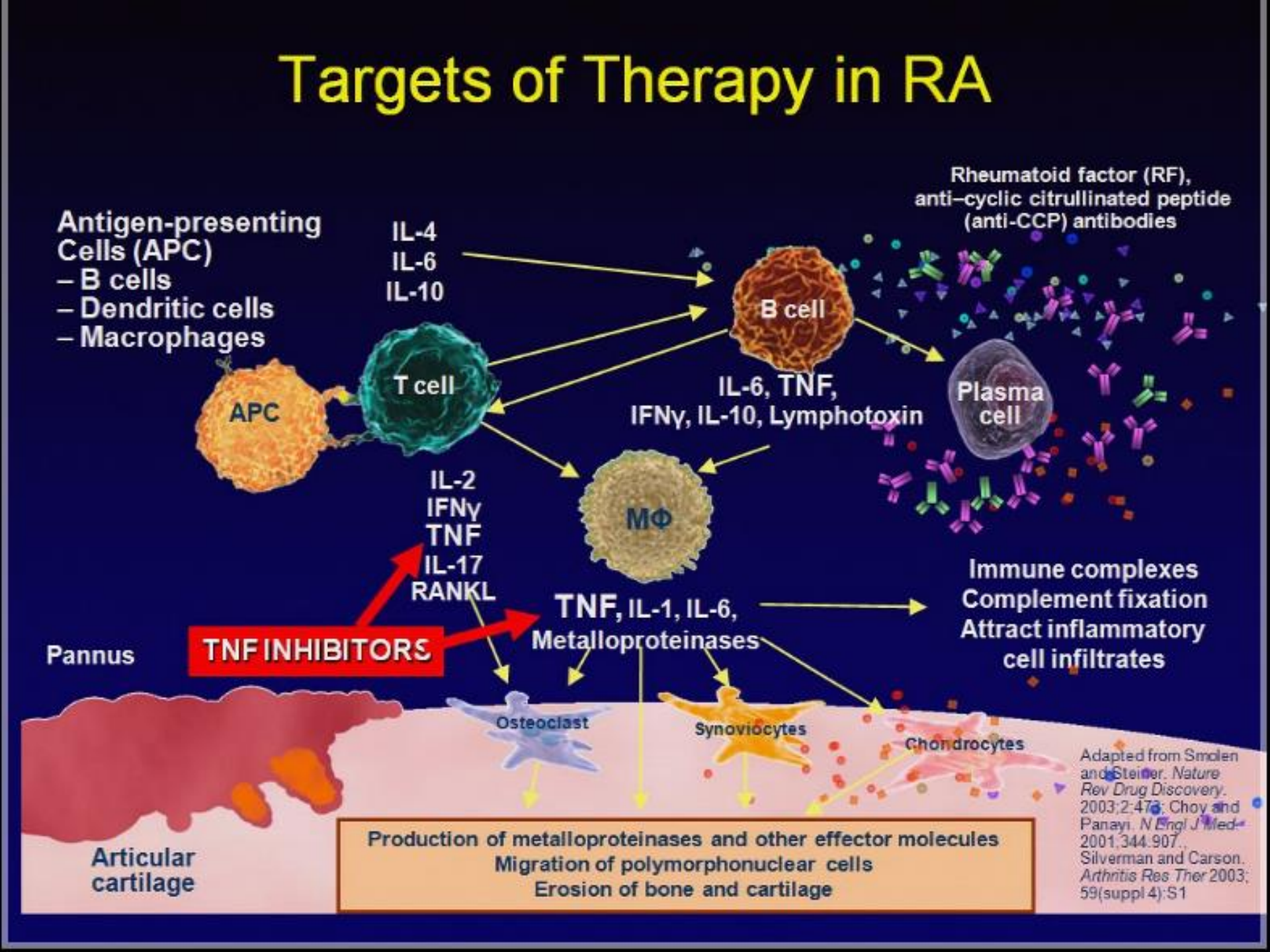
- Clinical and radiological remission : is it Reality or Fiction?

Introduction to Biologic Therapy

Achieve goals of treatment

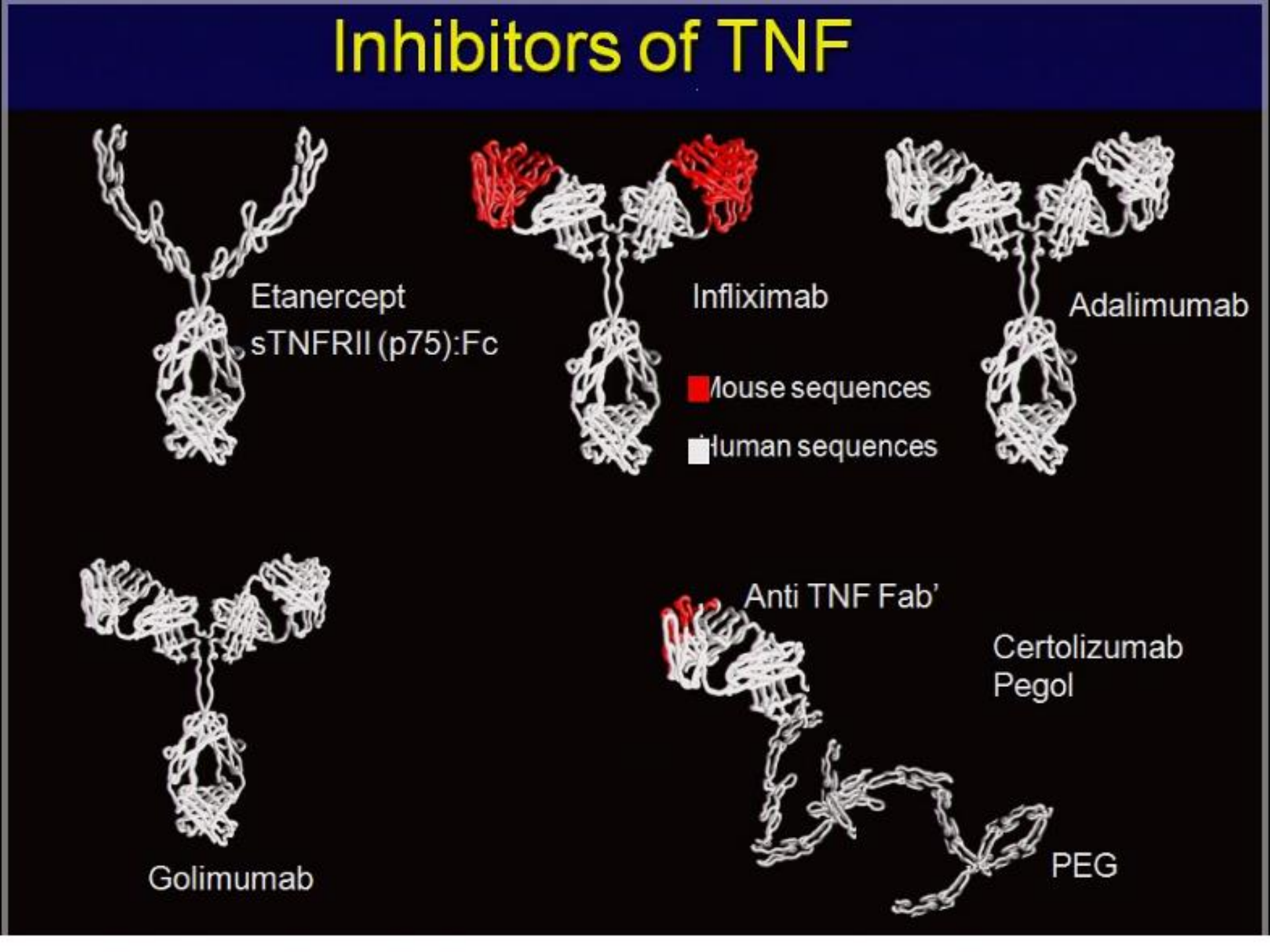
- Individualize treatment options
- Initiate treatment early
- Induction and maintenance of remission
- Use biologic as steroid and DMARD sparing agents
- Plan ahead for failure and withdrawal of therapy

Targets of Therapy in RA



Adapted from Smolen and Steiner. *Nature Rev Drug Discovery*. 2003;2:473; Choy and Panayi. *N Engl J Med*. 2001;344:907., Silverman and Carson. *Arthritis Res Ther* 2003; 59(suppl 4):S1

Inhibitors of TNF

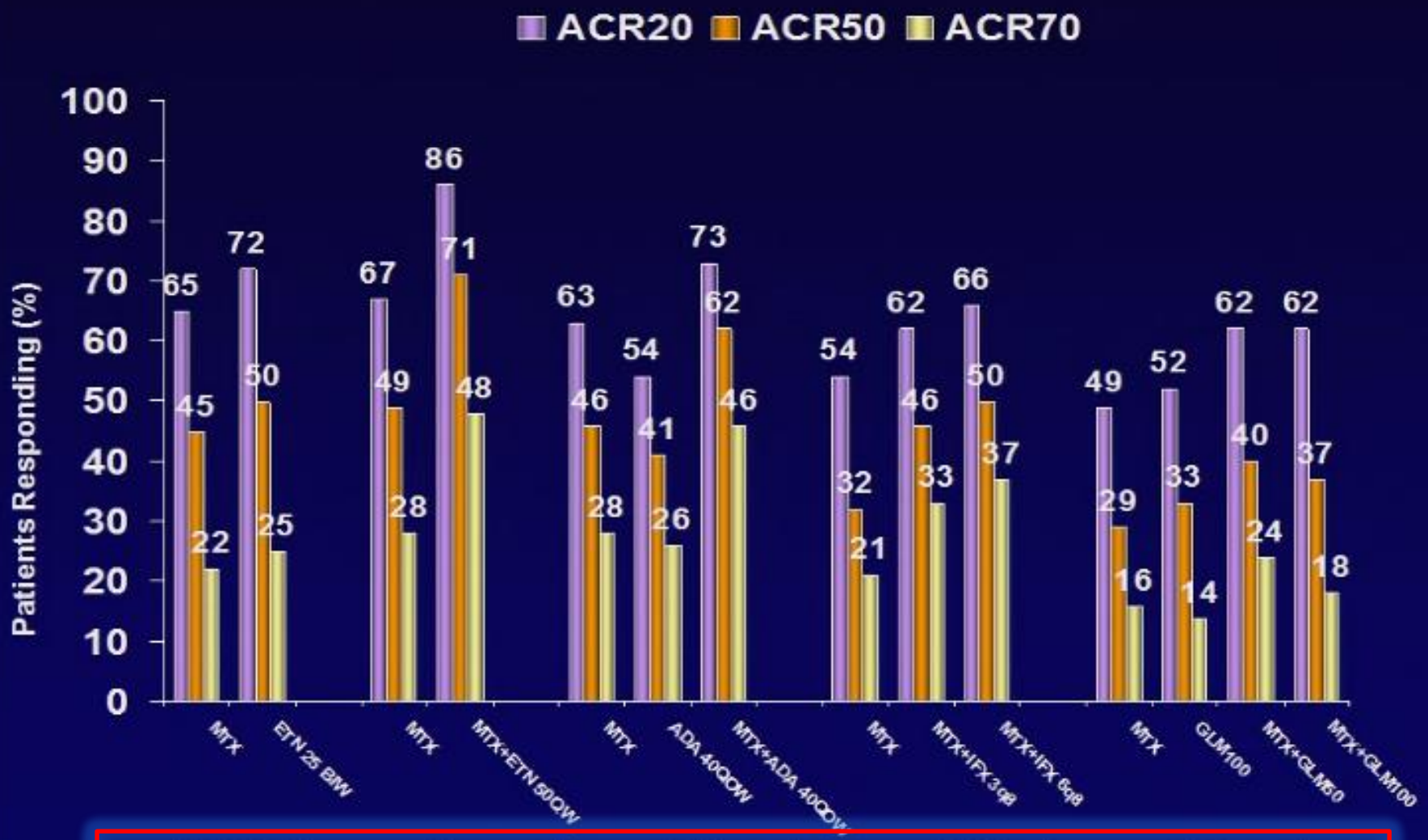


Characteristics of TNF Antagonists

Drug	Construct	Half-Life	Administration/ Dosing	Mechanism of Action
Adalimumab	Human monoclonal anti-TNF antibody	2 weeks	SC 40 mg every 2 wk (or every wk)	Binds soluble and cell bound TNF
Certolizumab pegol	Humanized, pegylated anti-TNF Fab' antibody	≈ 14 days	SC 400 mg, 0, 2, & 4 wk, then 200 mg q 2 wk or 400 mg q 4 wk	Binds to soluble and cell bound TNF
Etanercept	Soluble human p75 TNF receptor: Fc construct	102 ± 30 hrs	SC 50 mg q wk	Binds to soluble TNF; binds LT-α
Golimumab	Human monoclonal anti-TNF antibody	≈ 2 wk	SC 50 mg q month	Binds to soluble and cell bound TNF
Infliximab	Chimeric anti-TNF antibody	7.7 – 9.5 days	IV 3 mg/kg, 0, 2, 6 wk, then q 8 wk (including to 10 mg/kg up to every 6 wk)	Binds to soluble and cell bound TNF

Source: Prescribing information for these agents.

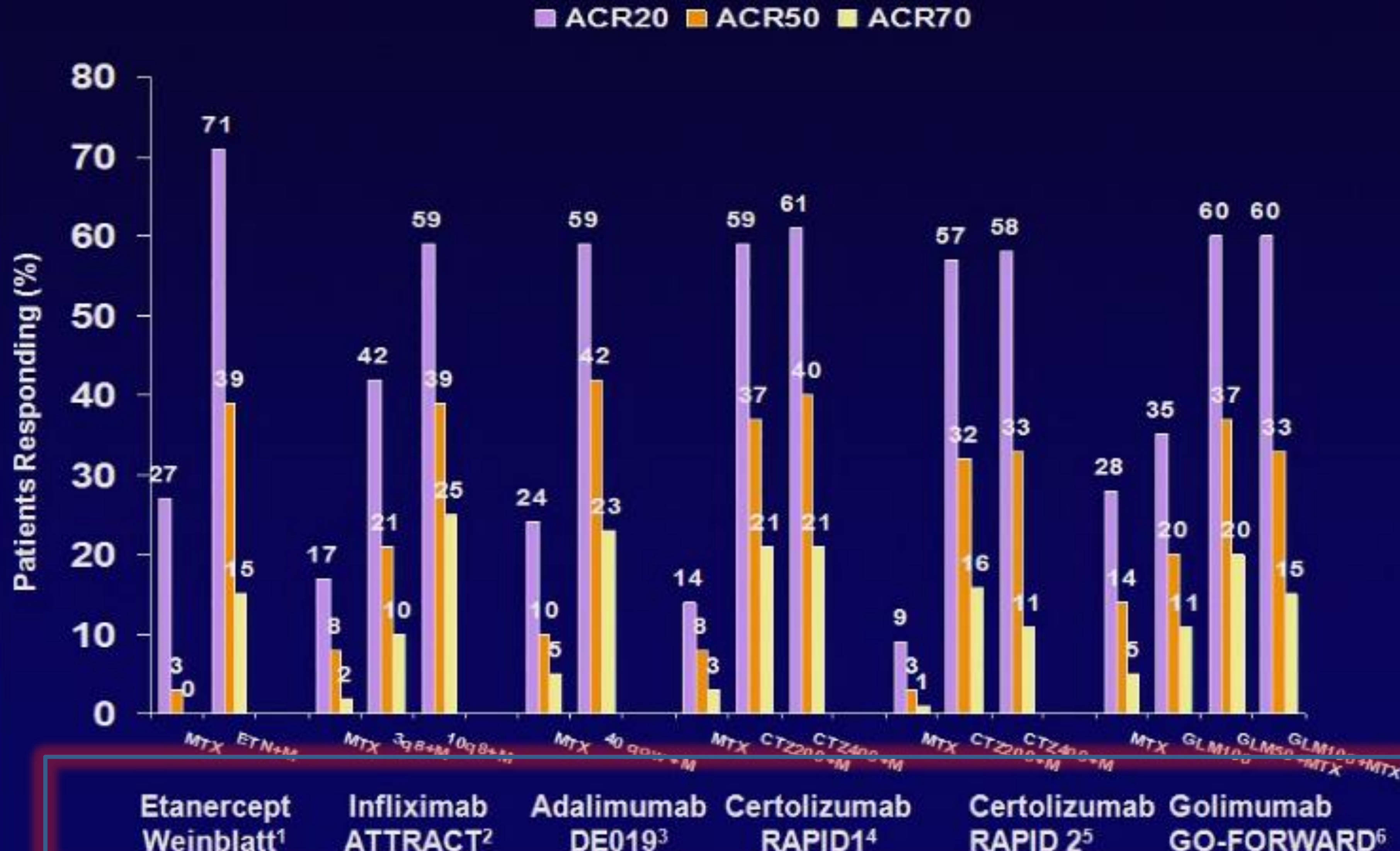
TNF Antagonists in Early RA



Etanercept	Etanercept	Adalimumab	Infliximab	Golimumab
ERA[1]	COMET[2]	PREMIER[3]	ASPIRE[4]	GO-BEFORE[5]

1. Bathon JM et al. *N Engl J Med*. 2000;343:1586-1593. 2. Emery P et al. *Lancet*. 2008;372:375-382. 3. Breedveld FC, et al. *Arthritis Rheum*. 2006;54:26-37. 4. St Clair EW et al. *Arthritis Rheum* . 2004;50:3432-3443. 5. Emery P et al. *Arthritis Rheum*. 2009;60:2272-2283.

TNF Antagonists Added to MTX: IRs



1. Weinblatt ME. *NEJM* 1999; 2. Lipsky PE. *NEJ M* 2000; 3. Keystone EC. *Clin Exp Rheumatol* 2003 ; 4. Keystone EC. *Arthritis Rheum* 2008; 5. Smolen JS. *Ann Rheum Dis* 2009. 6. Keystone E *Ann Rheum Dis*. 2009.

ARTHRITIS & RHEUMATISM
Vol. 54, No. 1, January 2006, pp 54–59
DOI 10.1002/art.21491

The Effectiveness of Anti–Tumor Necrosis Factor Therapy in Preventing Progressive Radiographic Joint Damage in Rheumatoid Arthritis

A Population-Based Study

Conclusion. **When combined with traditional DMARDs, both etanercept and infliximab appear to offer similar protection against progressive structural joint damage, and combination therapy with either of these agents appears to be more effective than treatment with etanercept alone.**

ARTHRITIS & RHEUMATISM
Vol. 50, No. 5, May 2004, pp 1400–1411
DOI 10.1002/art.20217

Radiographic, Clinical, and Functional Outcomes of Treatment With Adalimumab (a Human Anti–Tumor Necrosis Factor Monoclonal Antibody) in Patients With Active Rheumatoid Arthritis Receiving Concomitant Methotrexate Therapy

A Randomized, Placebo-Controlled, 52-Week Trial

Conclusion. **In this 52-week trial, adalimumab was more effective than placebo at inhibiting the progression of structural joint damage, reducing the signs and symptoms, and improving physical function in patients with active RA who had demonstrated an incomplete response to MTX.**

Optimizing the dosage

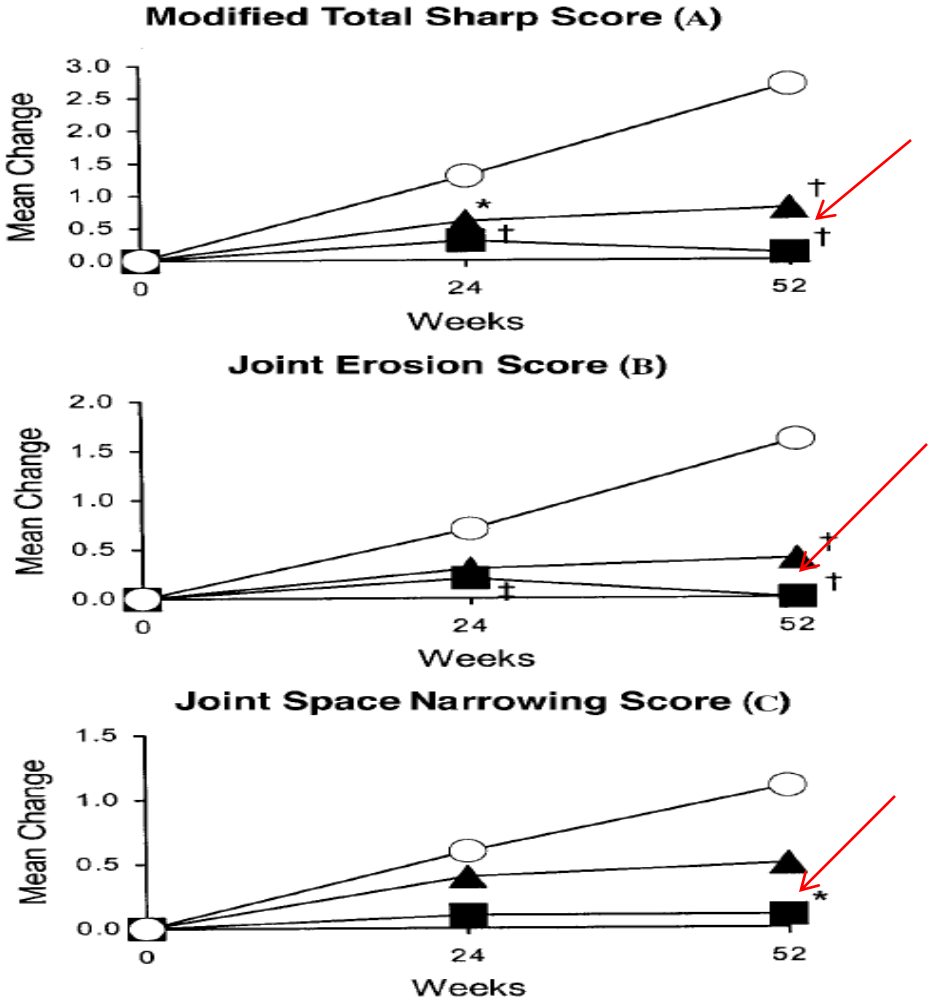
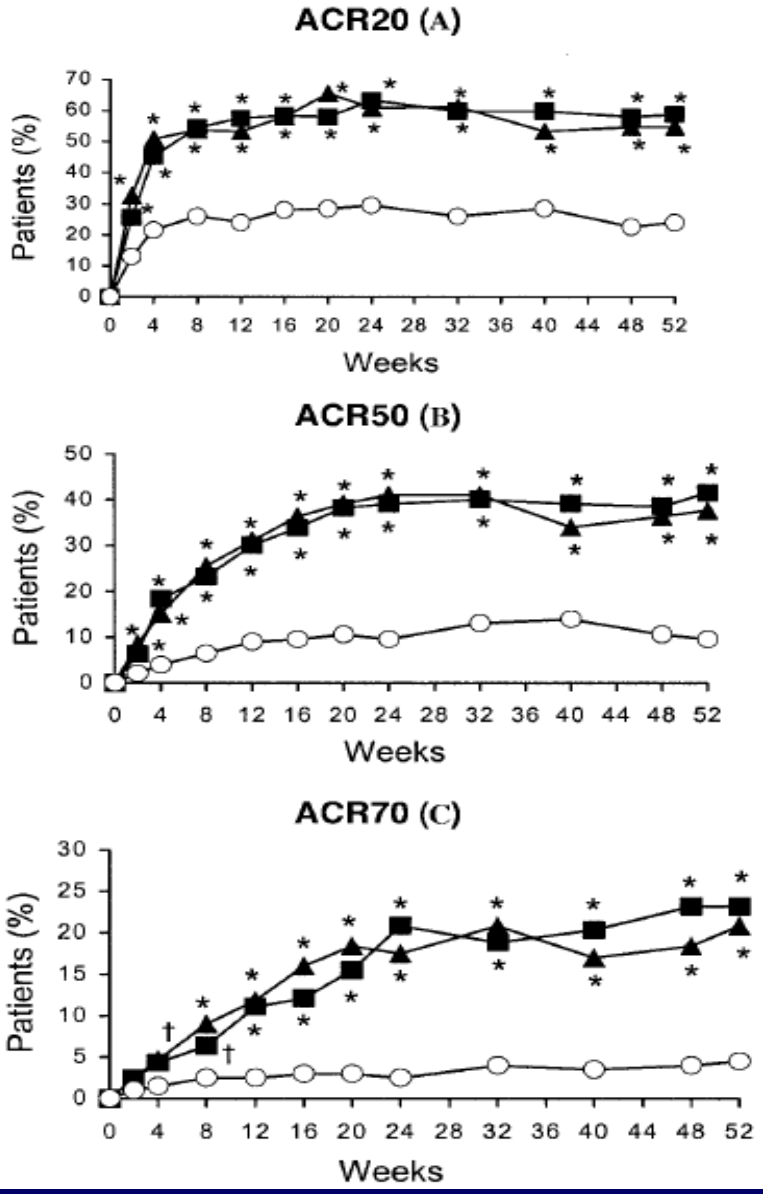


Figure 2. Changes from baseline to week 52 in the modified total Sharp radiographic progression scores (extrapolated data) (A), erosion scores (last observation carried forward [LOCF] data) (B), and joint space narrowing scores (LOCF data) (C) among the patients receiving adalimumab 40 mg every other week plus methotrexate (MTX) (■), adalimumab 20 mg weekly plus MTX (▲), and placebo plus MTX (○). * = $P \leq 0.01$, † = $P \leq 0.001$, and ‡ = $P \leq 0.05$ versus placebo (by analysis of covariance with the baseline value as the covariate).



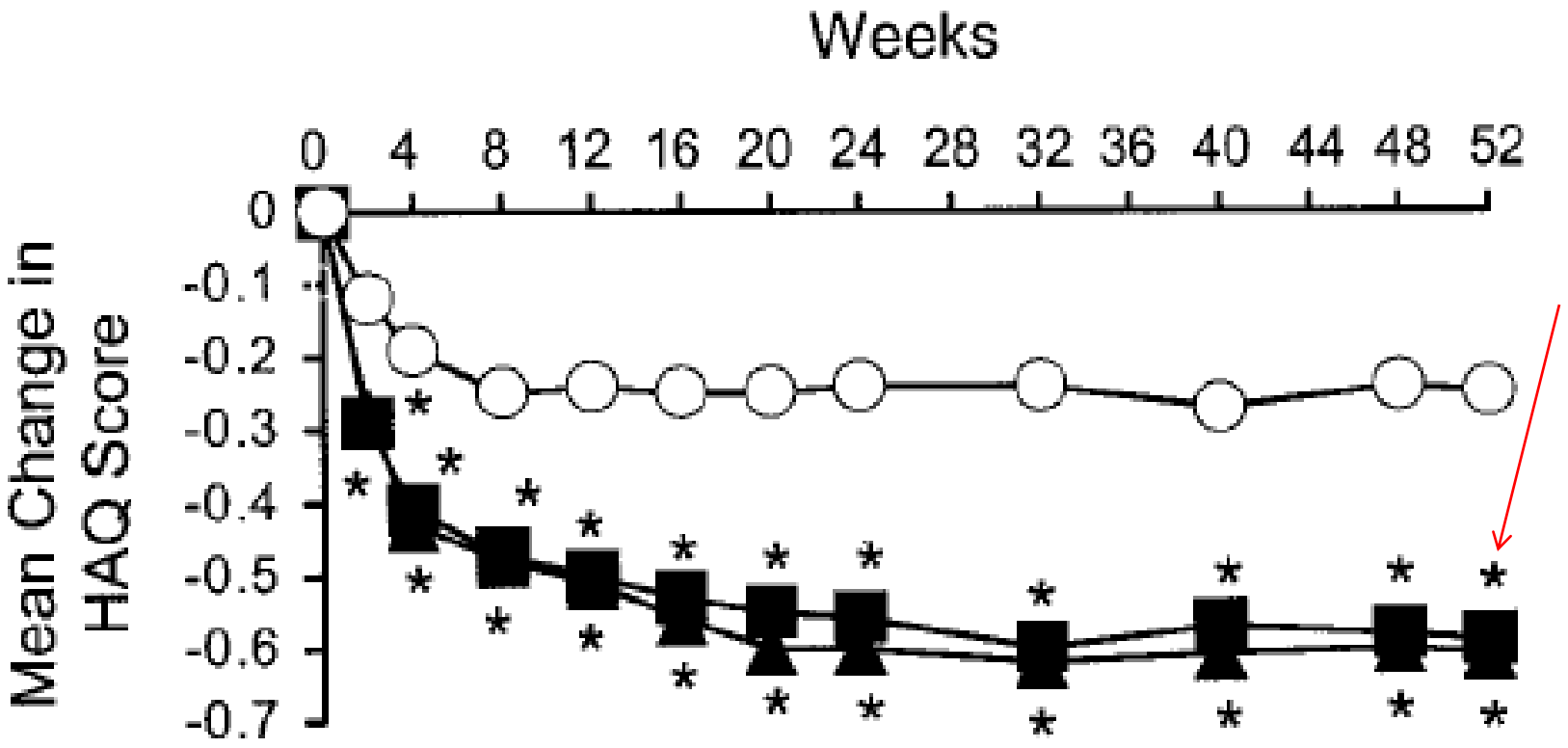


Figure 4. Changes in the Health Assessment Questionnaire (HAQ) scores (last observation carried forward data) among the patients receiving adalimumab 40 mg every other week plus methotrexate (MTX) (■), adalimumab 20 mg weekly plus MTX (▲), and placebo plus MTX (○). * = $P \leq 0.001$ versus placebo (by analysis of covariance with the baseline value as the covariate).

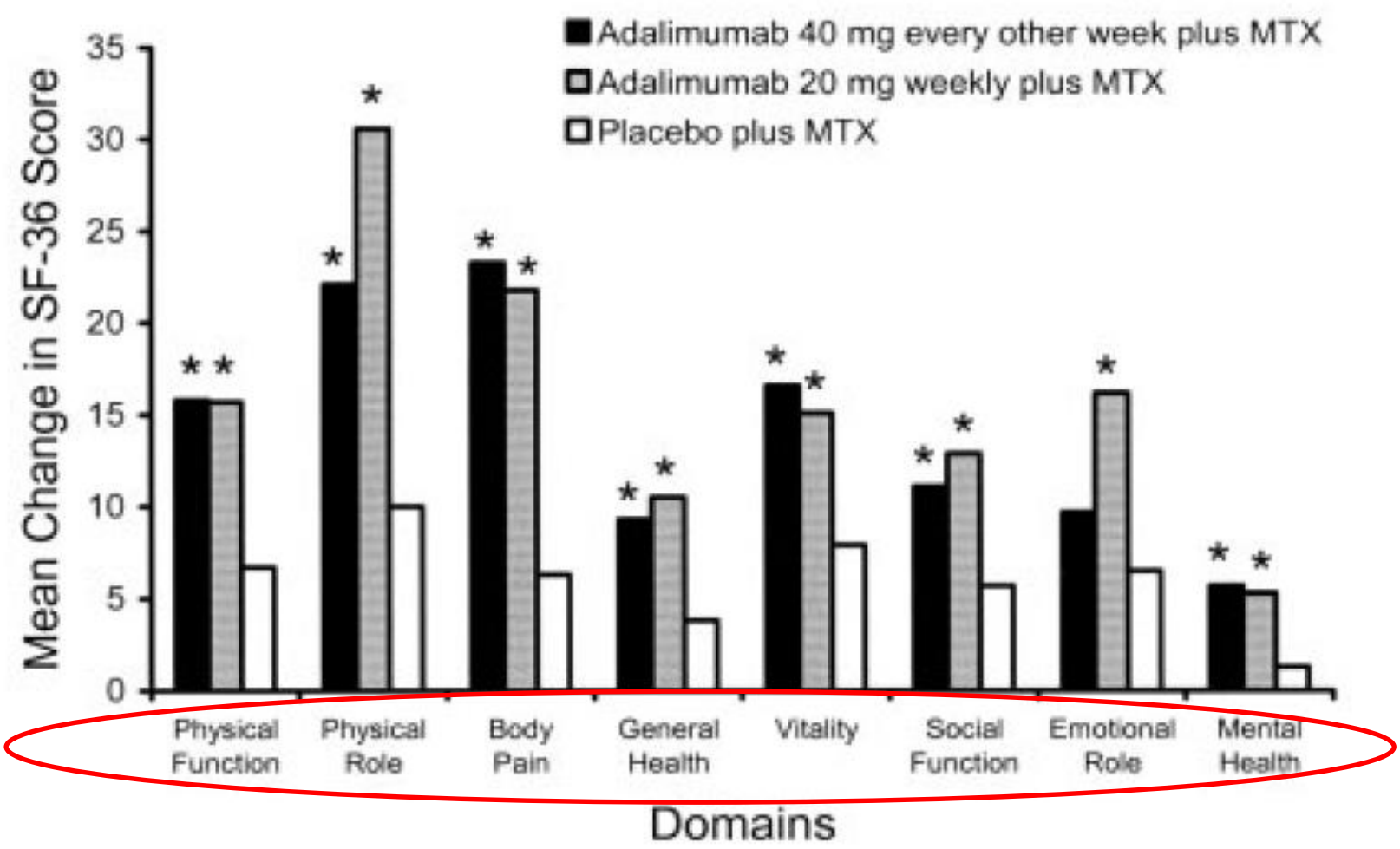


Figure 5. Changes in the Medical Outcomes Study Short Form 36-item health survey (SF-36) scores (last observation carried forward data). $* = P \leq 0.05$ versus placebo (by analysis of covariance with the baseline value as the covariate). MTX = methotrexate.

ARTHRITIS & RHEUMATISM
Vol. 52, No. 1, January 2005, pp 27–35
DOI 10.1002/art.20712

Very Early Treatment With Infliximab in Addition to Methotrexate in Early, Poor-Prognosis Rheumatoid Arthritis Reduces Magnetic Resonance Imaging Evidence of Synovitis and Damage, With Sustained Benefit After Infliximab Withdrawal

Results From a Twelve-Month Randomized, Double-Blind, Placebo-Controlled Trial

Table 1. Baseline demographics of the treatment groups*

	Infliximab plus MTX (n = 10)	Placebo plus MTX (n = 10)
Age, mean ± SD years	51.3 ± 9.5	53.1 ± 13.7
Symptom duration, mean ± SD months	7.4 ± 4.6	6 ± 3.7
RF positive, %	70	60
CRP, mean ± SD mg/liter	47 ± 27.9	37 ± 38.8
HAQ score, median (IQR)	1.3 (0.875)	1.3 (0.97)

* MTX = methotrexate; RF = rheumatoid factor; CRP = C-reactive protein; HAQ = Health Assessment Questionnaire; IQR = interquartile range.

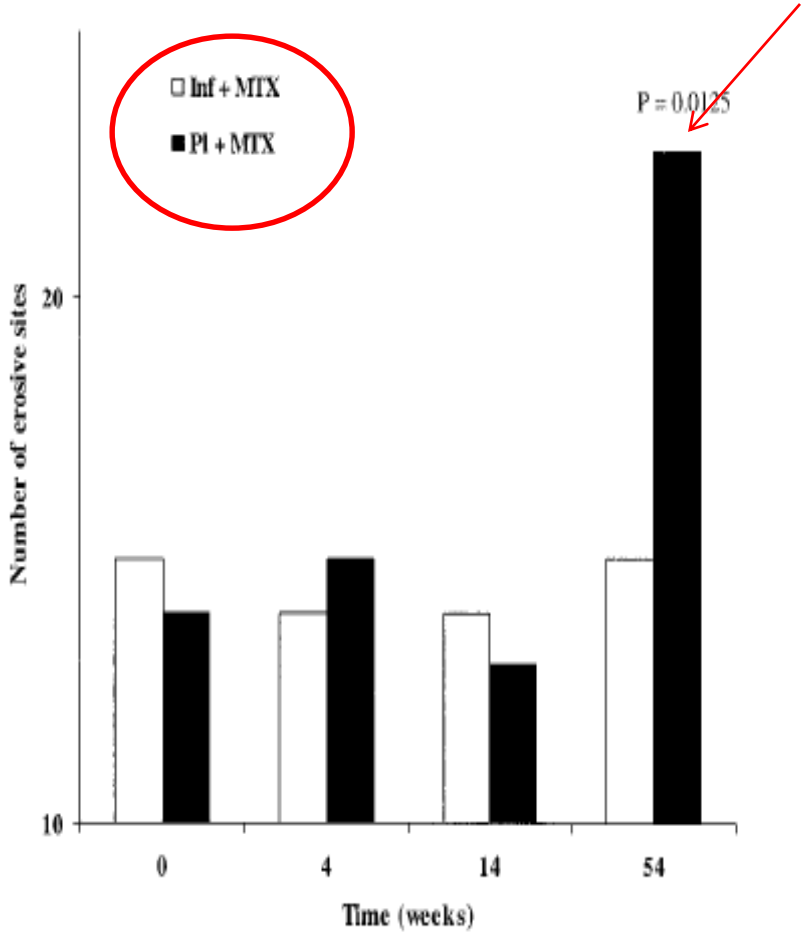


Figure 1. Comparison of metacarpophalangeal joint erosions identified by magnetic resonance imaging in the infliximab (Inf) plus methotrexate (MTX) group and the placebo (Pl) plus MTX group from baseline to week 54.

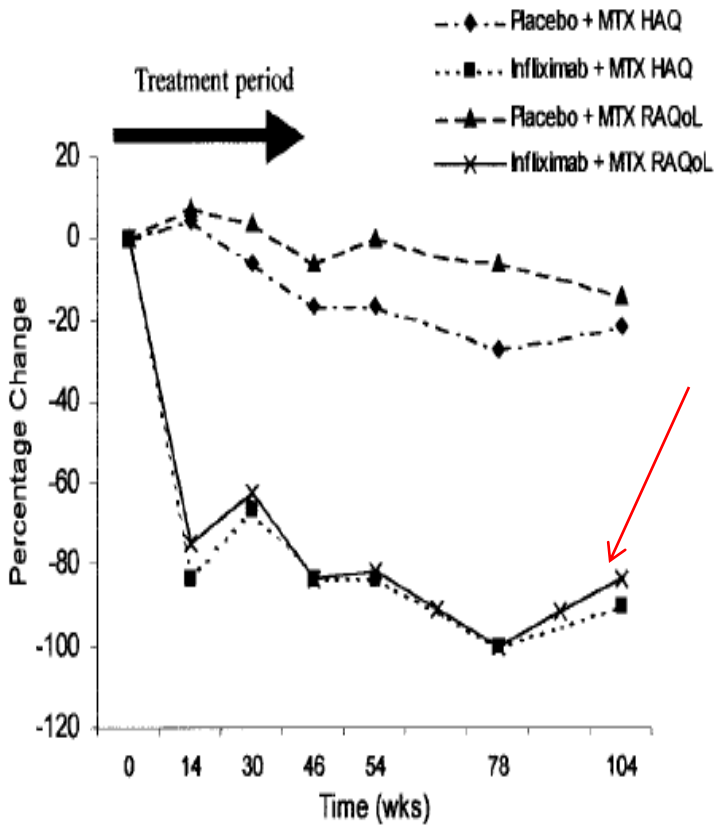


Figure 4. Percentage change in the median functional (by Health Assessment Questionnaire [HAQ]) and quality of life (by the Rheumatoid Arthritis Quality of Life [RAQoL] questionnaire) scores over time in the infliximab (Inf) plus methotrexate (MTX) group and the placebo (Pl) plus MTX group.

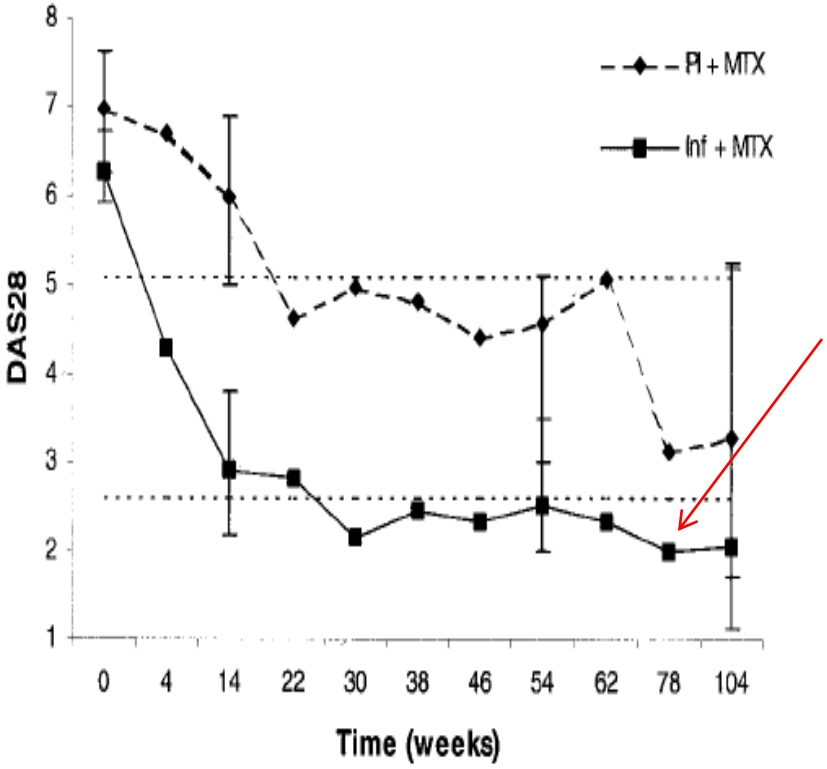


Figure 2. Changes in the Disease Activity Score in 28 joints (DAS28) over time in the infliximab (Inf) plus methotrexate (MTX) group and the placebo (Pl) plus MTX group. Values are the median and interquartile range.

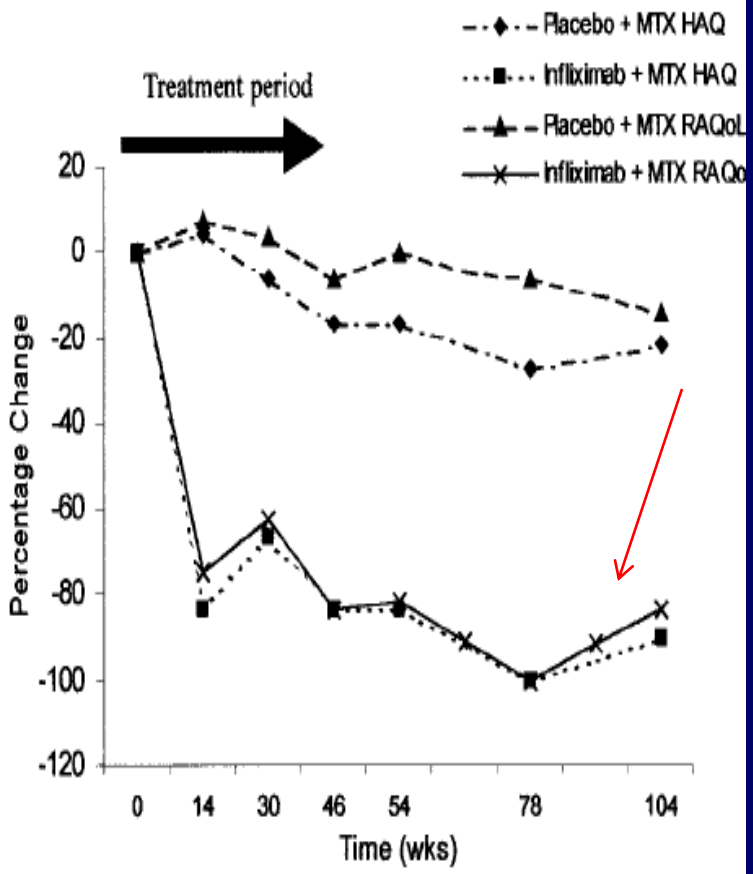


Figure 4. Percentage change in the median functional (by Heal Assessment Questionnaire [HAQ]) and quality of life (by the Rhe matoid Arthritis Quality of Life [RAQoL] questionnaire) scores ov

Maintenance of remission

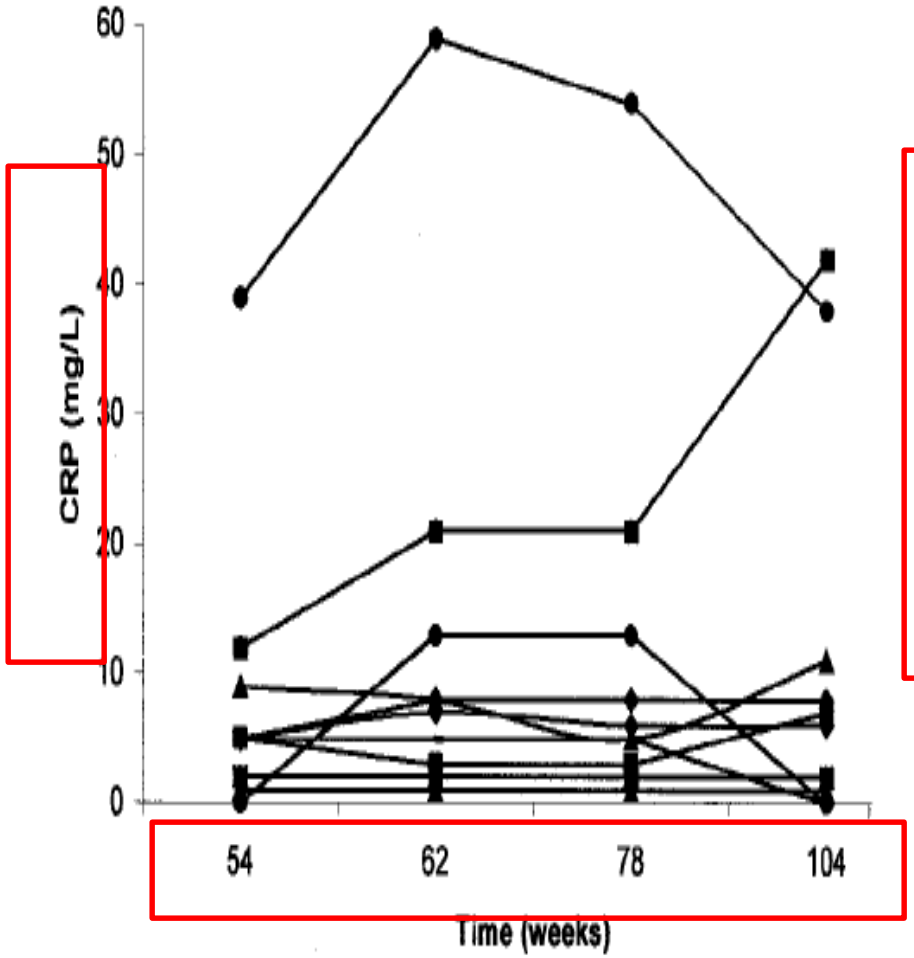


Figure 5. Levels of C-reactive protein (CRP) in individual patients treated with infliximab plus methotrexate after withdrawal of infliximab at 54 weeks.

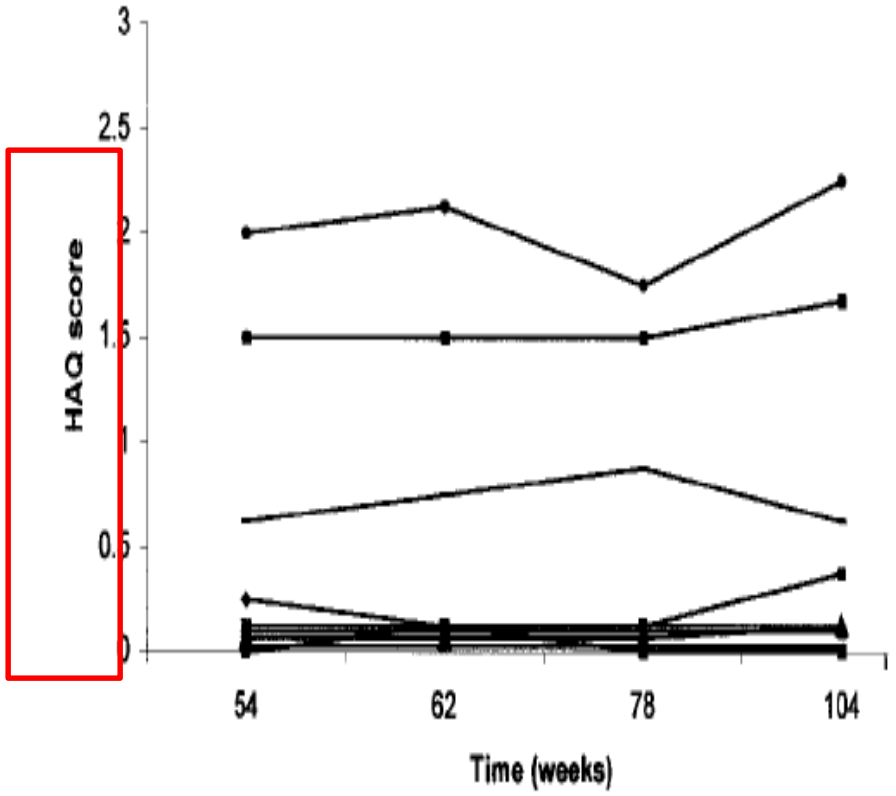


Figure 7. Health Assessment Questionnaire (HAQ) scores in individual patients treated with infliximab plus methotrexate after withdrawal of infliximab at 54 weeks.

Introduction of Ultrasound

ARTHRITIS & RHEUMATISM
Vol. 58, No. 8, August 2008, pp 2248–2256
DOI 10.1002/art.23682

Power Doppler Ultrasonographic Monitoring of Response to Anti–Tumor Necrosis Factor Therapy in Patients With Rheumatoid Arthritis

Conclusion. **These findings indicate that PDUS is a valid method for monitoring response to anti-TNF therapy in RA; results obtained by PDUS are reproducible and sensitive to change. PDUS findings may have predictive value in relation to radiologic outcome.**

Detecting Neovascularization

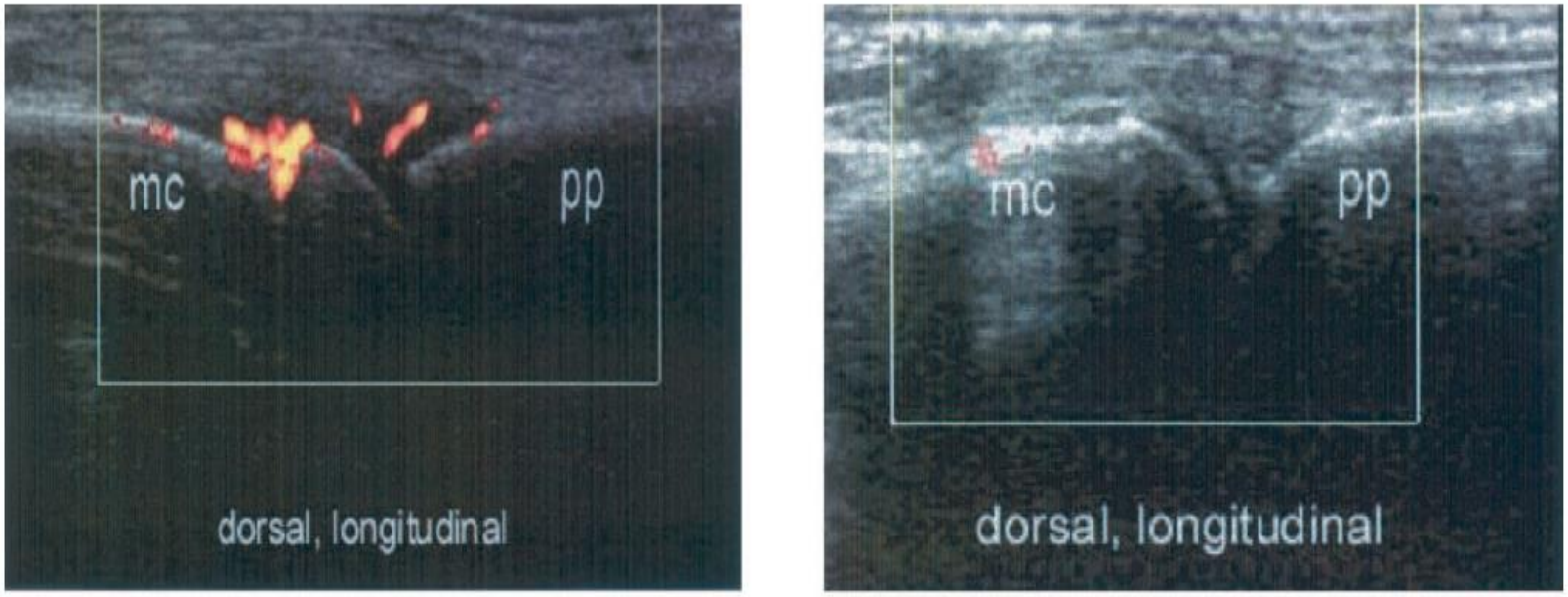


Figure 2. Ultrasound (US) images of a metacarpophalangeal joint obtained at baseline (**A**) and after 1 month of anti–tumor necrosis factor therapy (**B**). US performed before the initiation of therapy showed moderate synovial fluid, synovial hypertrophy, and synovial power Doppler signal, whereas after 1 month of therapy the joint appeared normal, with resolution of the earlier pathologic findings. **mc** = metacarpal bone; **pp** = proximal phalanx.

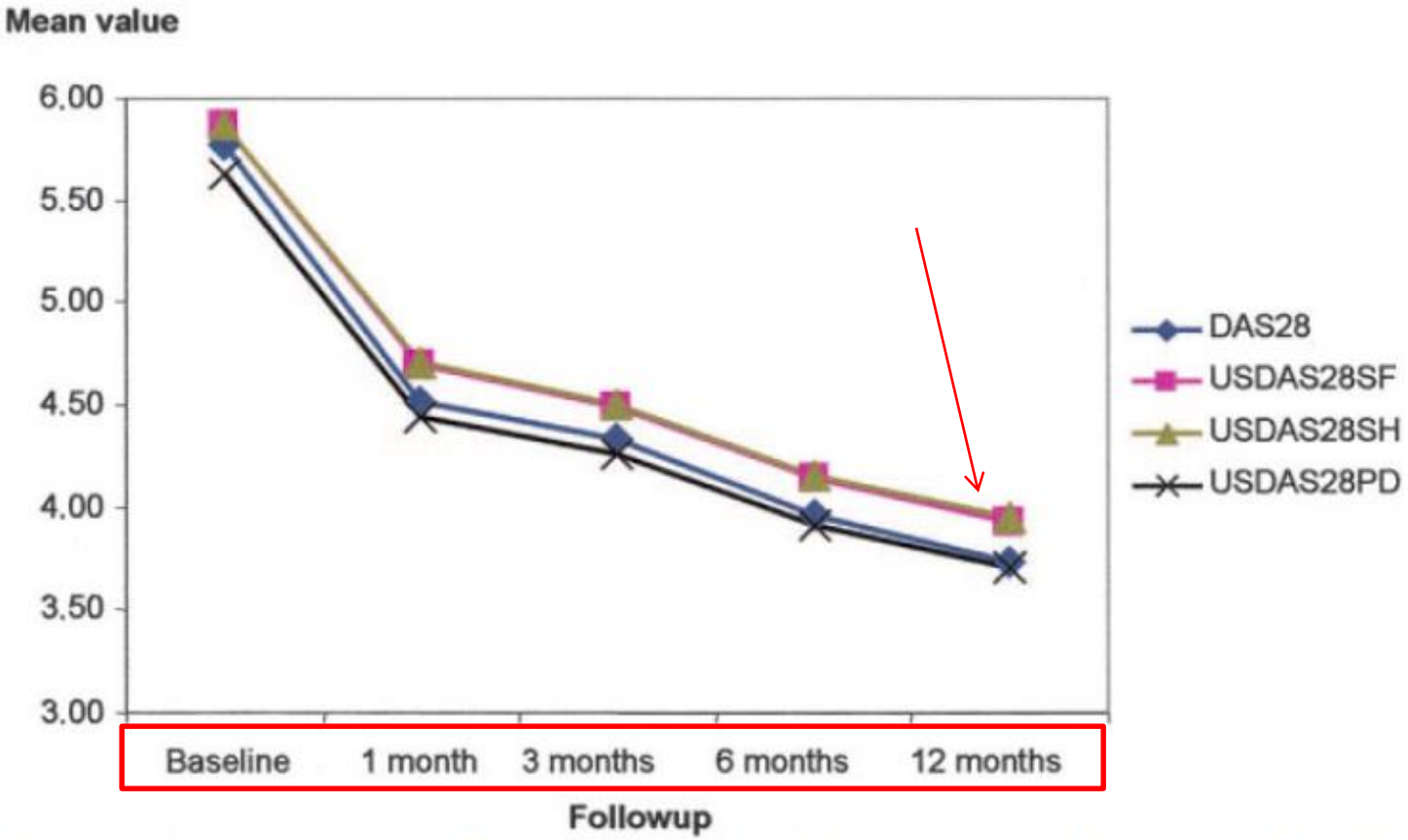


Figure 1. Changes in the Disease Activity Score in 28 joints (DAS28) and the modified ultrasonographic DAS28 with synovial fluid, synovial hypertrophy, and power Doppler signal (USDAS28 SF, USDAS28 SH, and USDAS28 PD, respectively) throughout the followup period, in 278 rheumatoid arthritis patients receiving anti–tumor necrosis factor therapy.

ARTHRITIS & RHEUMATISM
Vol. 50, No. 4, April 2004, pp 1107–1116
DOI 10.1002/art.20123

Comparison of Ultrasonographic Assessment of Synovitis and Joint Vascularity With Radiographic Evaluation in a Randomized, Placebo-Controlled Study of Infliximab Therapy in Early Rheumatoid Arthritis

Conclusion. **The delay or reversal of inflammatory and joint-destructive mechanisms in patients with early RA was already apparent following 18 weeks of treatment with infliximab + MTX and was reflected in radiologic changes at 54 weeks.**

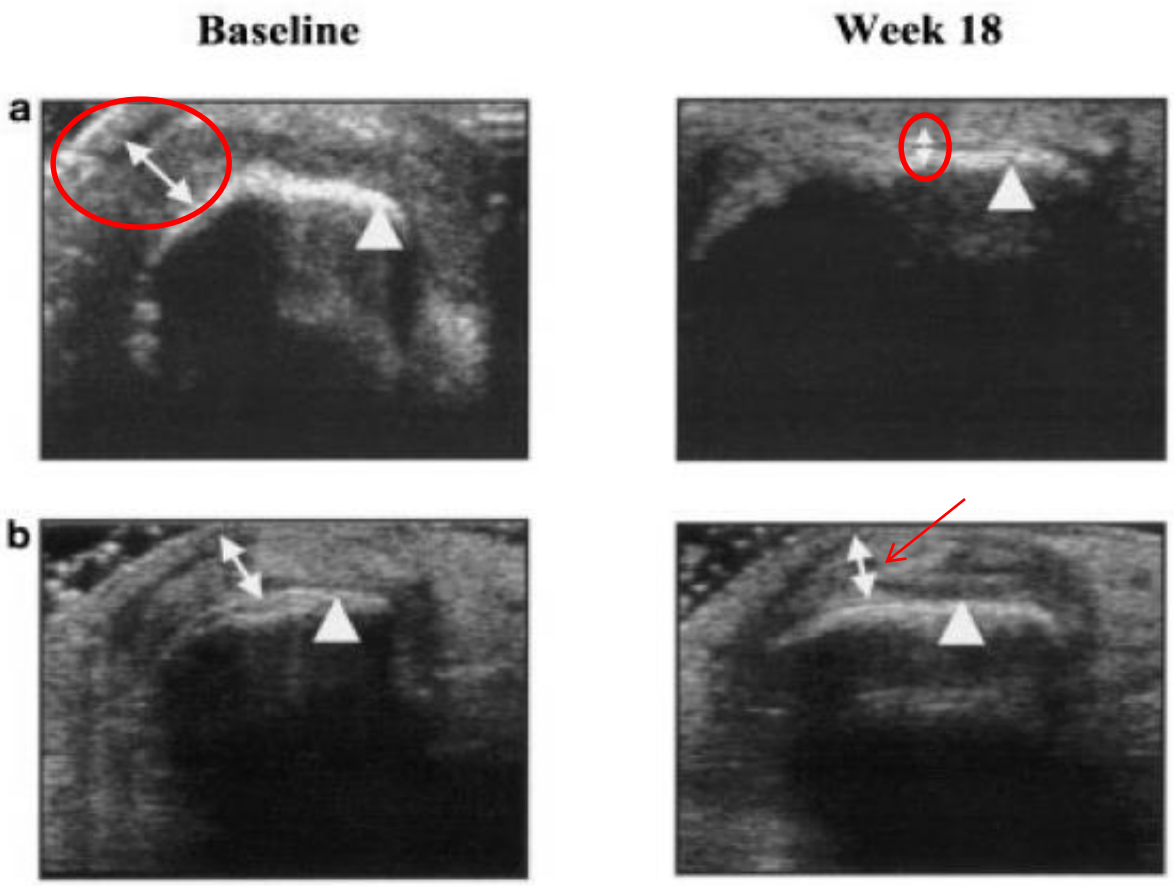


Figure 2. High-frequency ultrasound images of the second metacarpophalangeal joint in the transverse plane, depicting examples of **a,** good and **b,** poor responders with respect to changes in synovial thickening. Synovium is represented by an anechoic or a hypoechoic region over the dorsum of the joint (**double-headed arrows**). **Arrowheads** indicate the metacarpal head.

What this talk is about

- What if anti TNF therapy fails

Identify non responders

Table 1. Clinical characteristics at baseline and after 2 years of followup*

	Responders (n = 67)	Patients requiring continued infliximab treatment (n = 23)	Patients in whom treatment failed (n = 30)	Overall *P*
DAS, mean ± SD				
Baseline	4.1 ± 0.7	4.3 ± 1	4.6 ± 0.9	0.04†
2 years	1.4 ± 0.6	2.2 ± 0.8	2.7 ± 0.8	<0.01‡
HAQ, mean ± SD				
Baseline	1.3 ± 0.7	1.2 ± 0.5	1.7 ± 0.6	<0.01§
2 years	0.3 ± 0.4	0.5 ± 0.5	0.9 ± 0.6	<0.01§
SHS, mean ± SD				
Baseline	6.9 ± 10.6	5.4 ± 5.6	7.8 ± 11.3	0.89
2 years	8.3 ± 11.2	7.9 ± 9.4	12.7 ± 14.6	0.29
SHS, median (IQR)				
Baseline	3.8 (1–7.1)	3.0 (1.5–7)	4.0 (0.9–10.6)	0.89
2 years	4.5 (1.5–11)	4.3 (0.8–13.1)	6.0 (2–24.5)	0.29
Change in SHS, mean ± SD	1.5 ± 3.4	2.9 ± 4.8	5.0 ± 6	0.01†
Change in SHS, median (IQR)	0.5 (0–2)	1.5 (0–4.4)	2.5 (0–7)	0.01†
% of patients with SHS greater than or equal to the SDC after 2-year followup	9.4	20	37	<0.01†

* DAS = Disease Activity Score; HAQ = Health Assessment Questionnaire; SHS = modified Sharp/van der Heijde score; IQR = interquartile range; SDC = smallest detectable change.
† = $P = 0.01$, responders versus patients in whom treatment failed, by Mann-Whitney U test.
‡ = $P < 0.01$, responders versus continued infliximab treatment group and versus patients in whom treatment failed, by Mann-Whitney U test.
§ = $P < 0.01$, patients in whom treatment failed versus continued infliximab treatment group and versus responders, by one-way analysis of variance.

Joint damage even with anti TNF

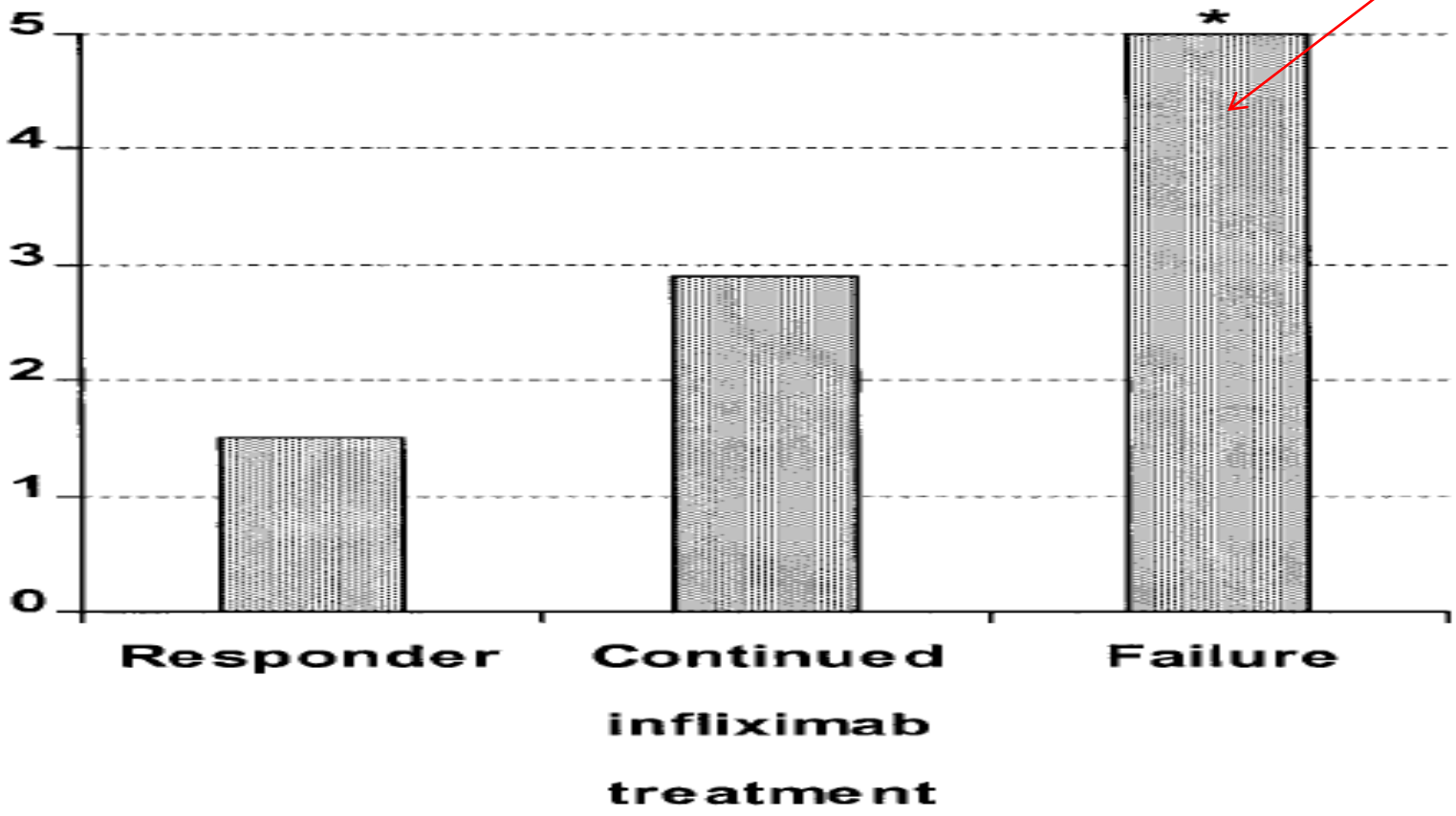


Figure 2. Mean change in the modified Sharp/van der Heijde score after 2 years of followup, showing greater progression of joint damage in the patients whose rheumatoid arthritis failed to respond to infliximab compared with those who were responders. * = $P < 0.01$ versus responders.

Sonograhpgic Doppler flow in non responder

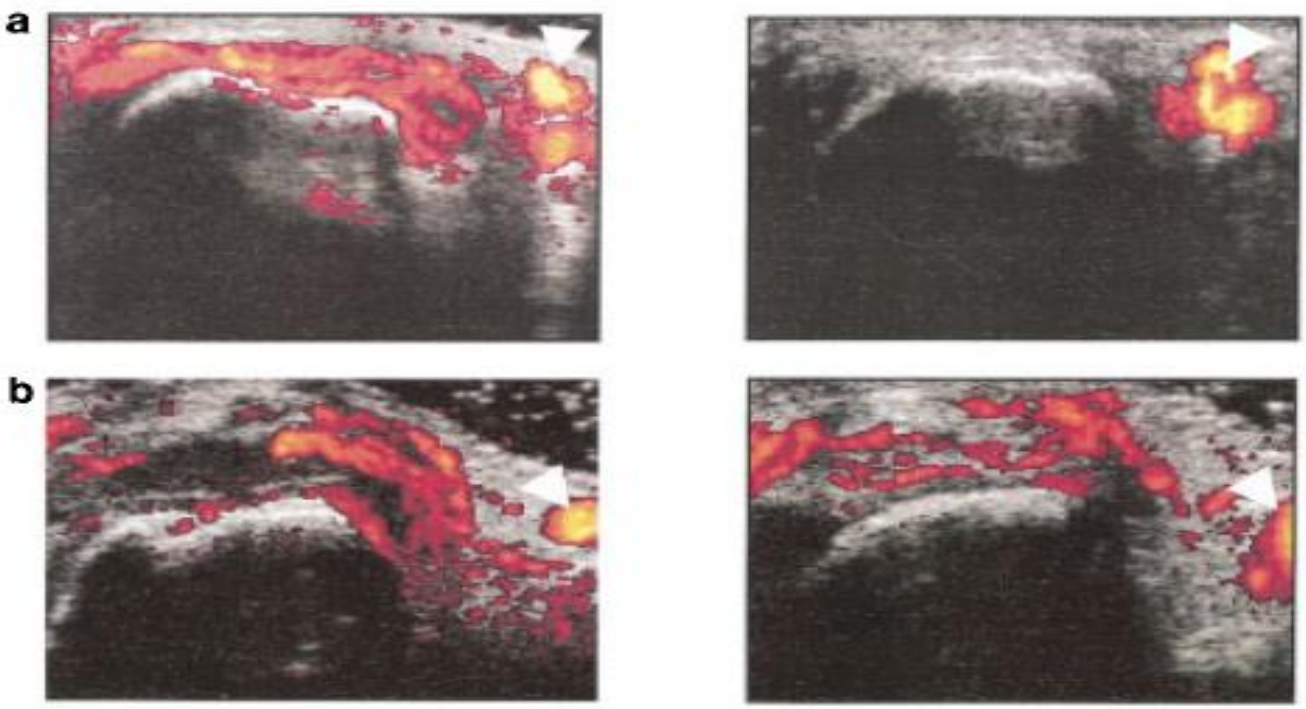
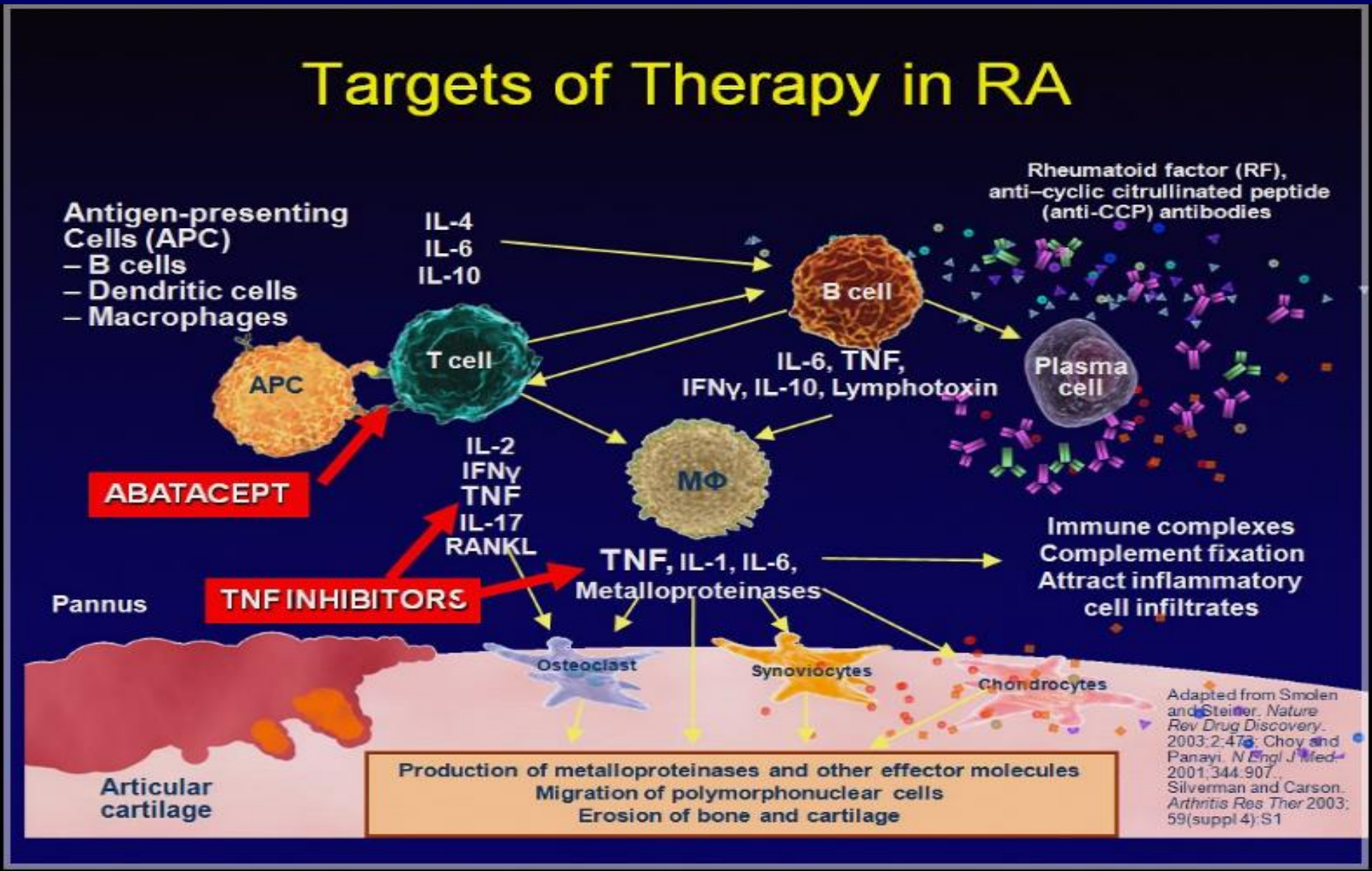


Figure 3. Power Doppler images of the second metacarpophalangeal joint in the transverse plane, depicting examples of **a**, good and **b**, poor responders with respect to changes in the color Doppler area. The strong vascular signal (**arrowheads**) represents a digital vessel.

ARTHRITIS & RHEUMATISM
Vol. 50, No. 4, April 2004, pp 1107–1116
DOI 10.1002/art.20123

Options for Anti TNF failures

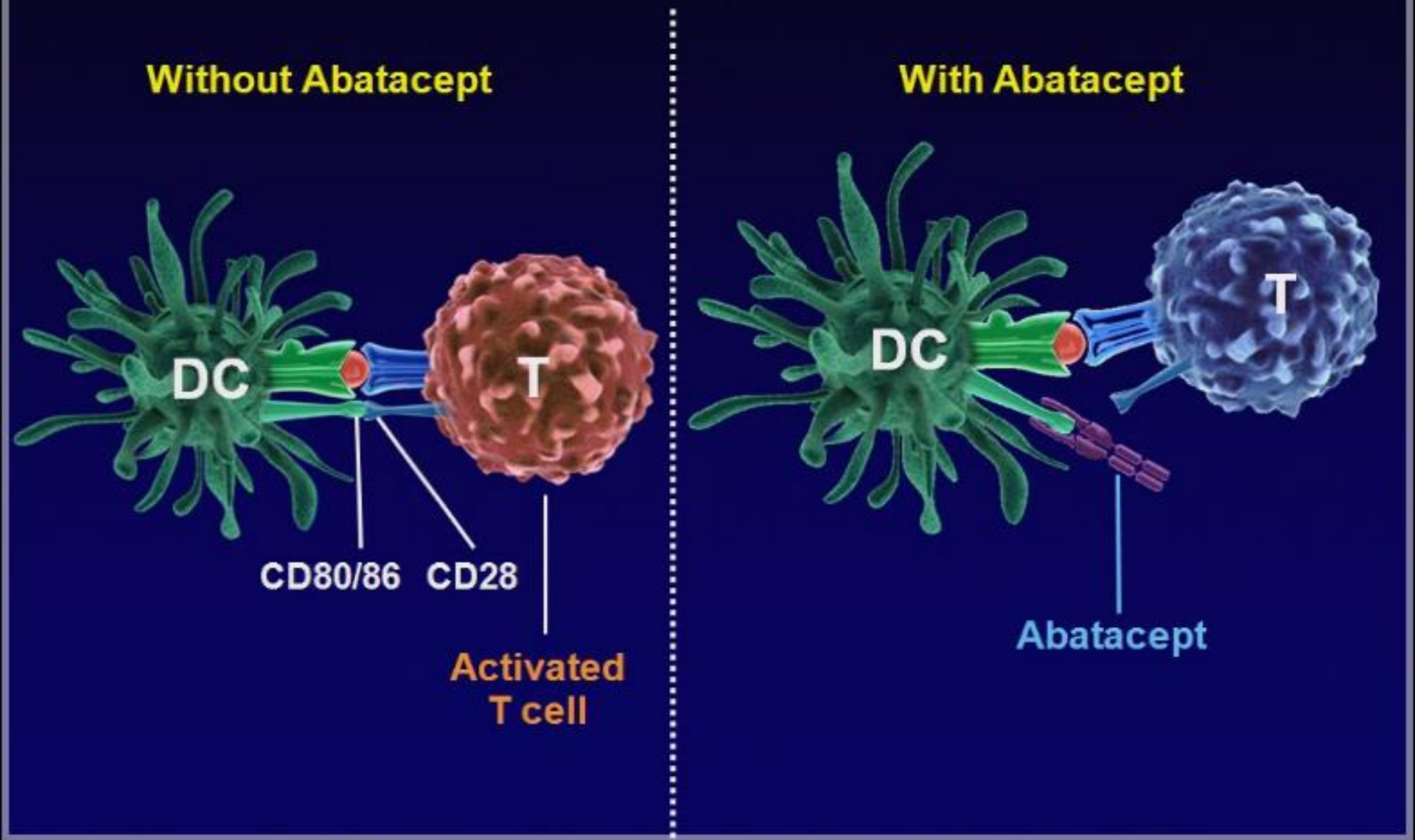


Other Biologic Agents

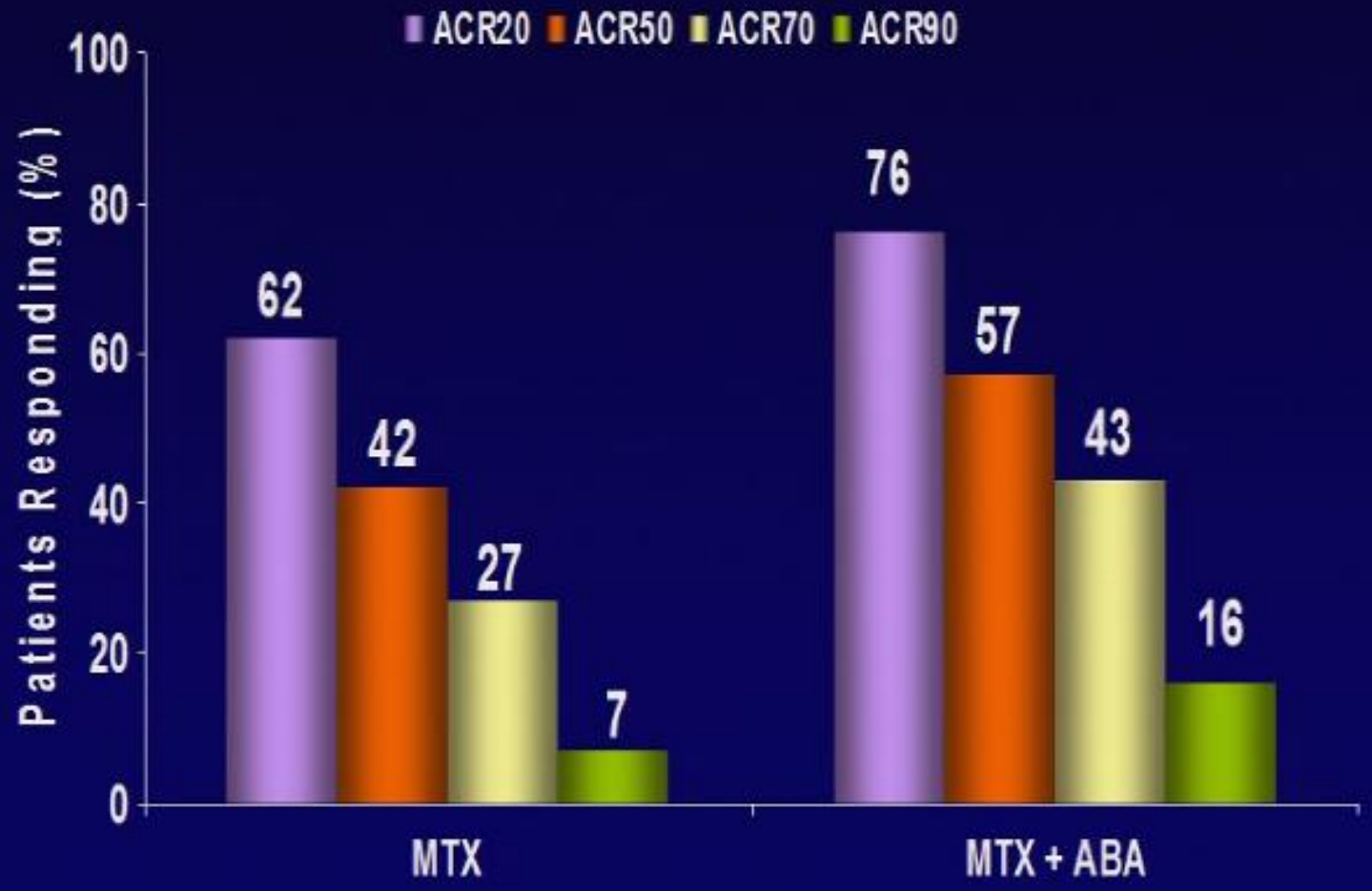
Drug	Construct	Target	Administration	Dosing Frequency
Abatacept	Soluble receptor: Fc	T cell costimulation (CD80/86-CD28)	IV	0, 2, 4 wk then q 4wk
Rituximab	Chimeric monoclonal antibody	B cells (CD20)	IV	0 and 2 wk then q 6 mo or prn
Tocilizumab	Humanized monoclonal antibody	IL-6 receptor	IV	q 4 wk
Anakinra	Receptor antagonist	IL-1 receptor	SC	Daily

Source: Prescribing information for these agents.

Mechanism of Action of Abatacept Inhibiting T-Cell Co-stimulation

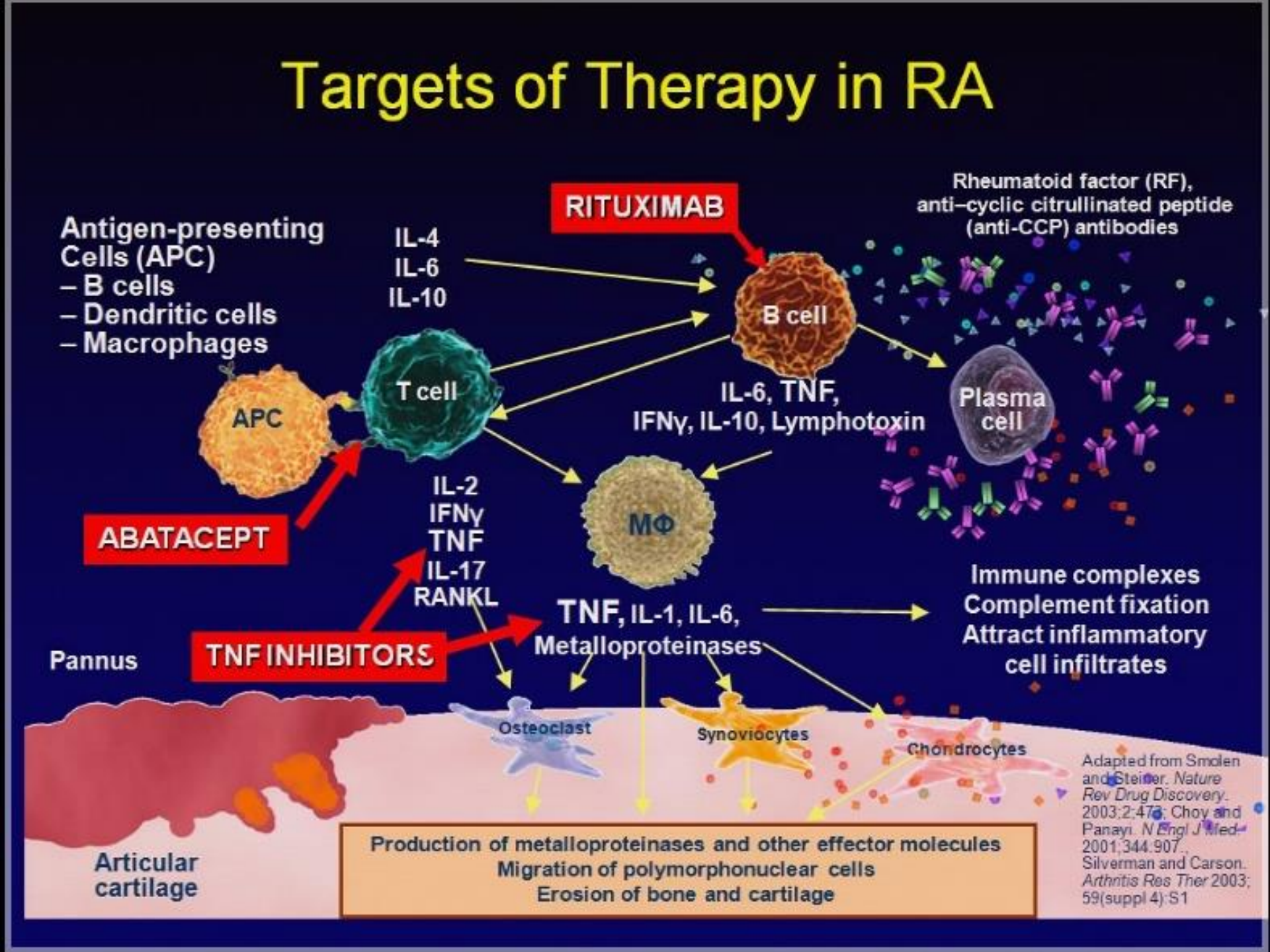


Costimulatory Blockade: Abatacept in Early RA (AGREE)



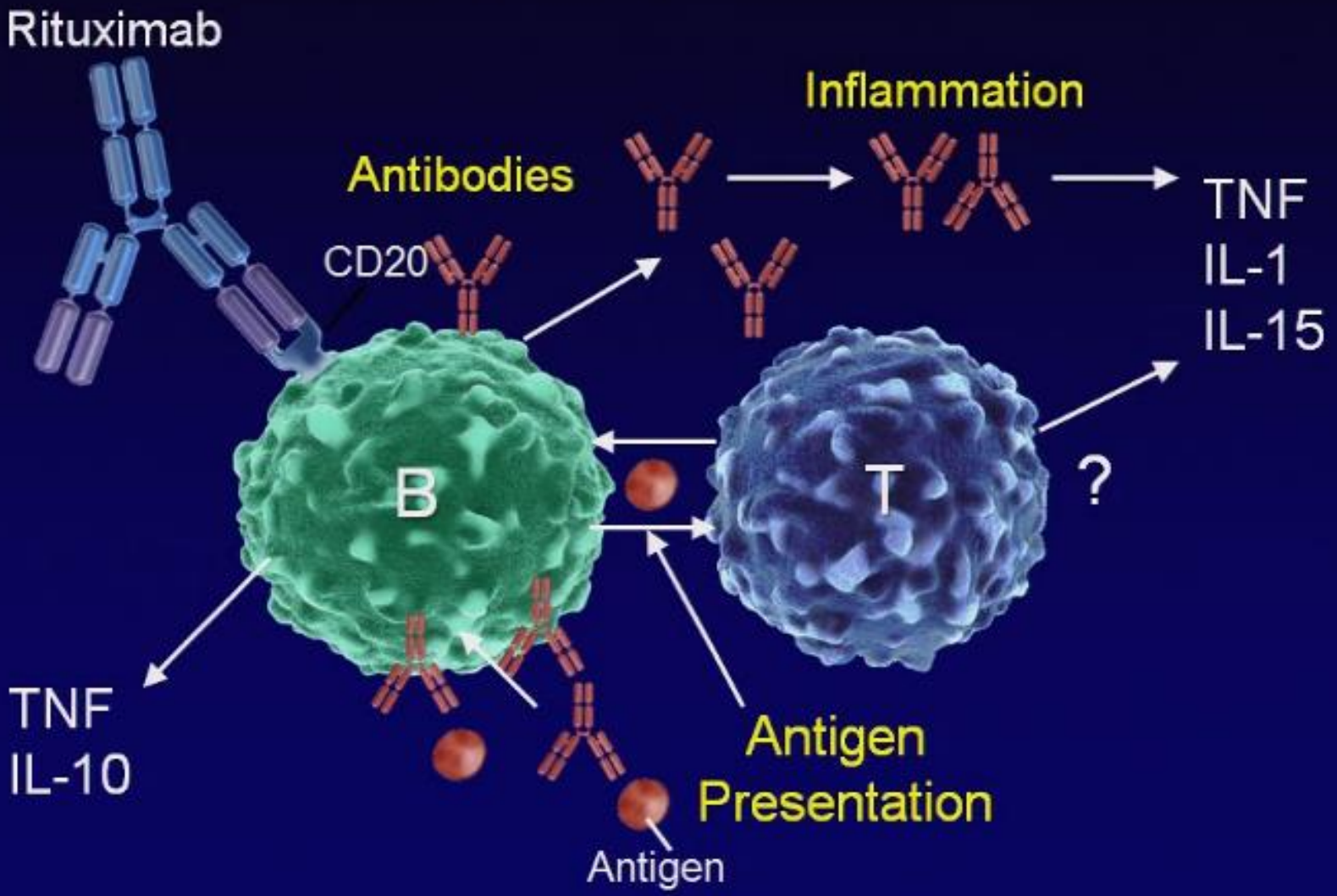
Westhovens R et al. *Ann Rheum Dis*. 2009 Dec;68(12):1870-7.

Targets of Therapy in RA

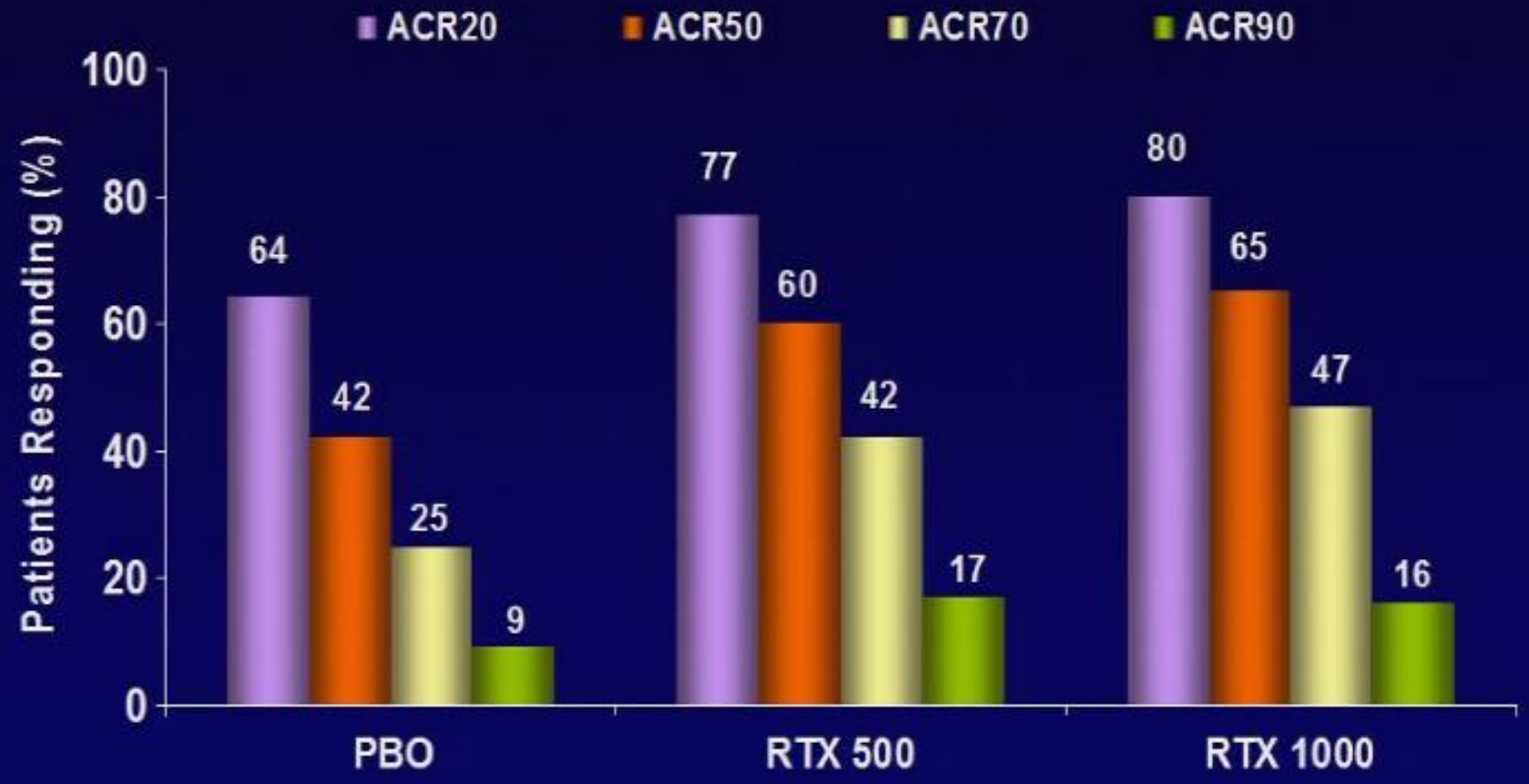


Adapted from Smolen and Steiner. *Nature Rev Drug Discovery*. 2003;2:473; Choy and Panayi. *N Engl J Med*. 2001;344:907., Silverman and Carson. *Arthritis Res Ther* 2003; 59(suppl 4):S1

Mechanism of Action of Rituximab Targeting B Cells



B Cell Inhibition: Rituximab in Early RA (IMAGE)

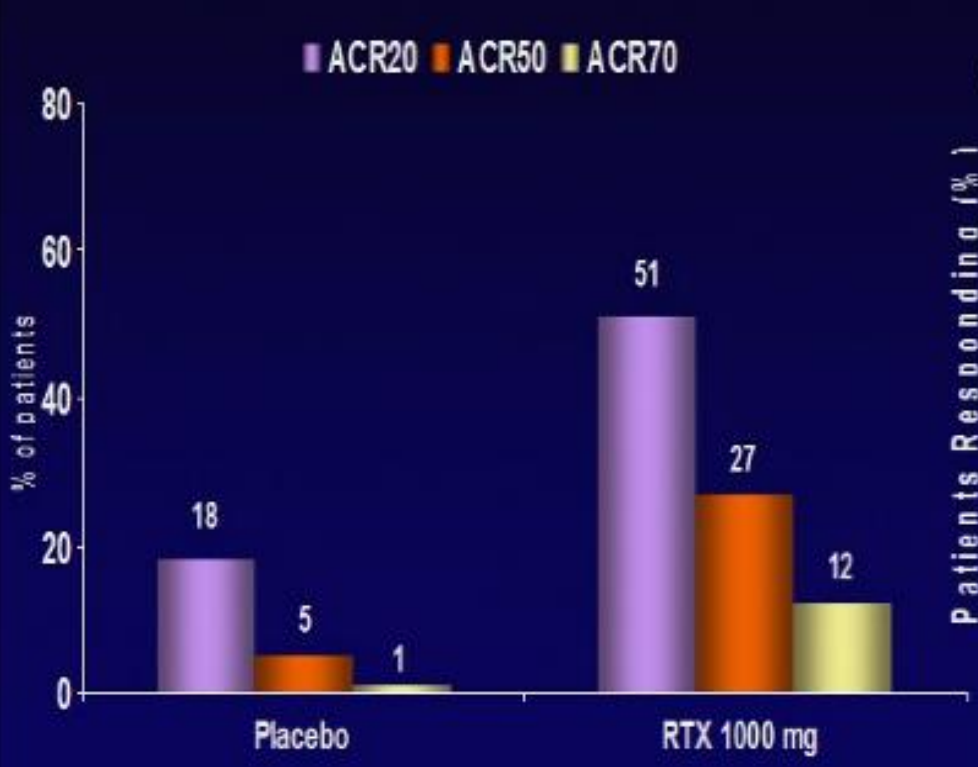


Tak PP et al. *Ann Rheum Dis*. 2009;68(suppl 3):75.

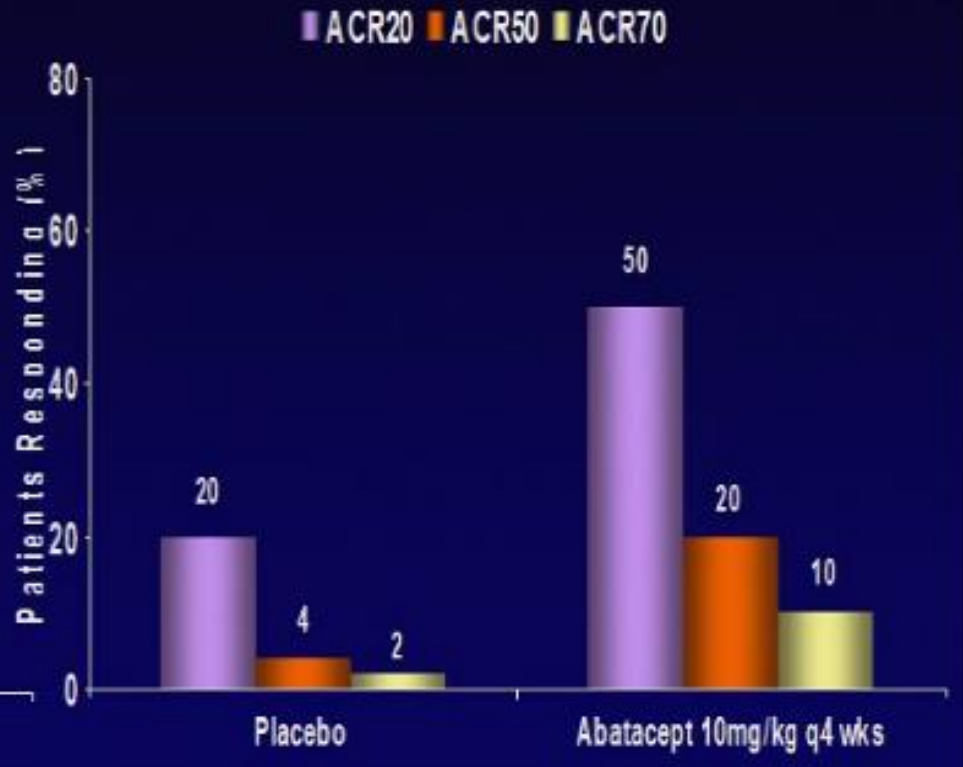
TNF Antagonist IRs:

Rituximab and Abatacept: 6-Month Data

Rituximab[1] (REFLEX) 6 Months

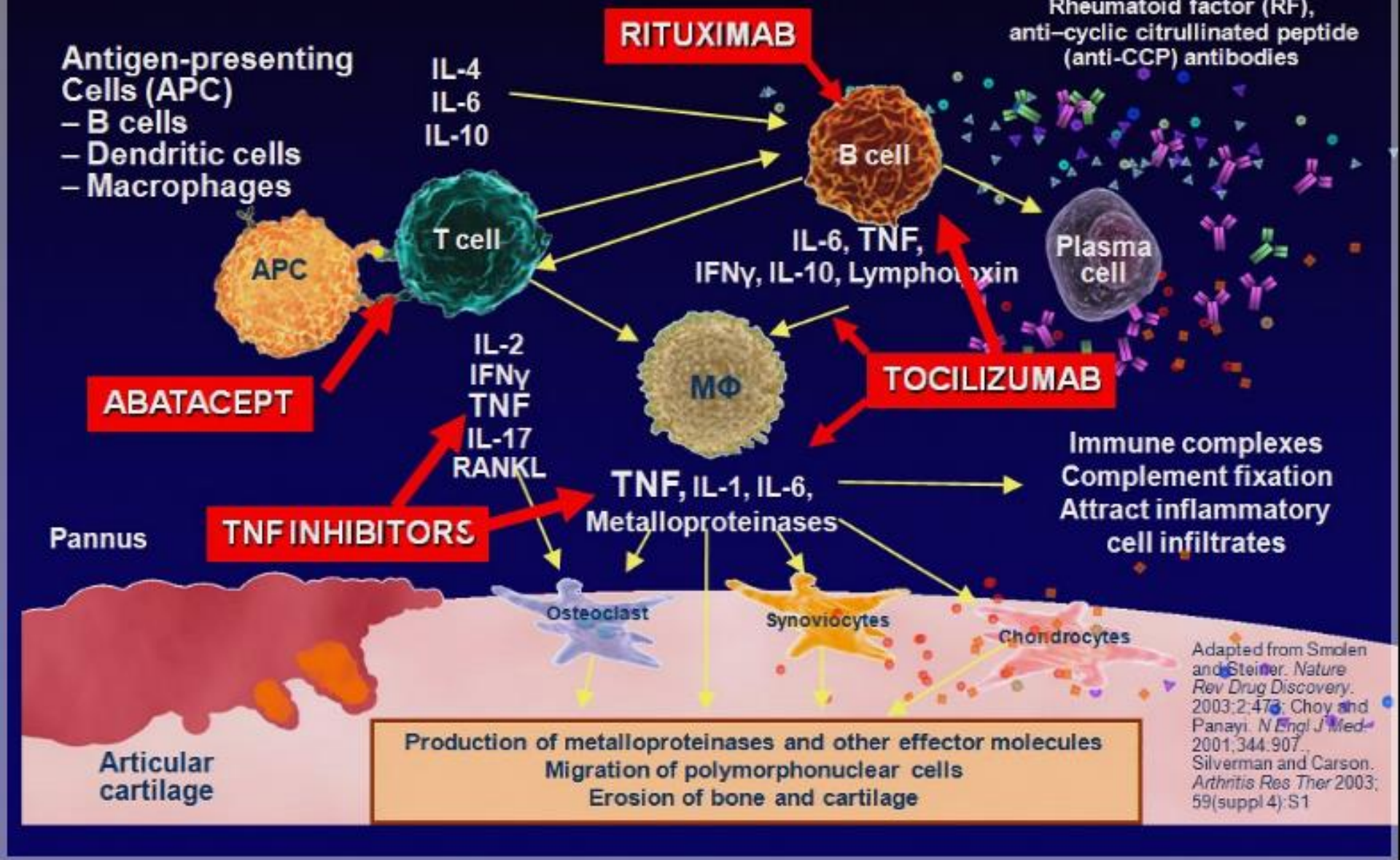


Abatacept[2] (ATTAIN) 6 Months



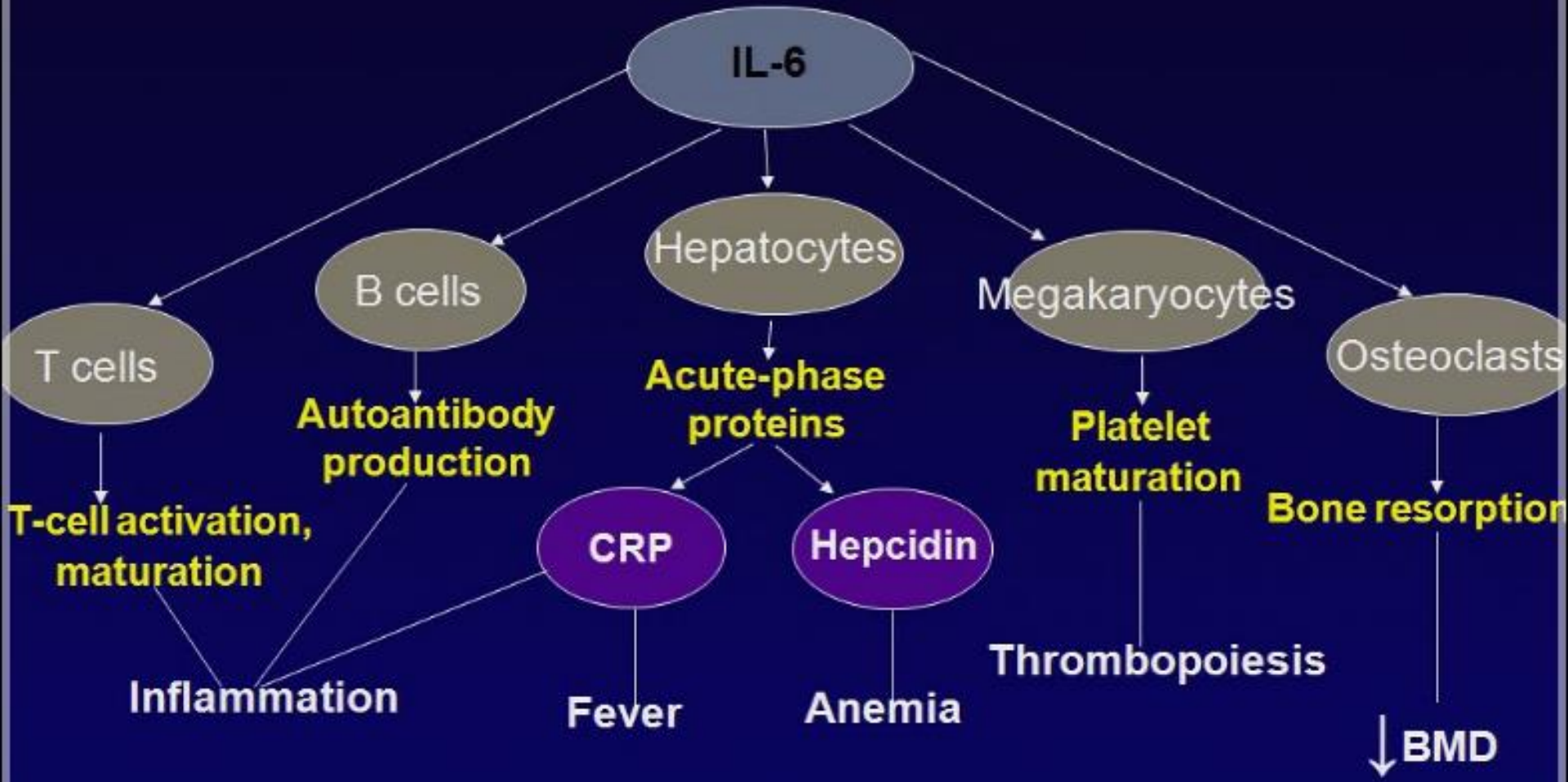
1. Cohen SB et al. *Arthritis Rheum.* 2006;54:2793-2806. 2. Genovese MC et al. *N Engl J Med.* 2005;353:1114-1123.

Targets of Therapy in RA



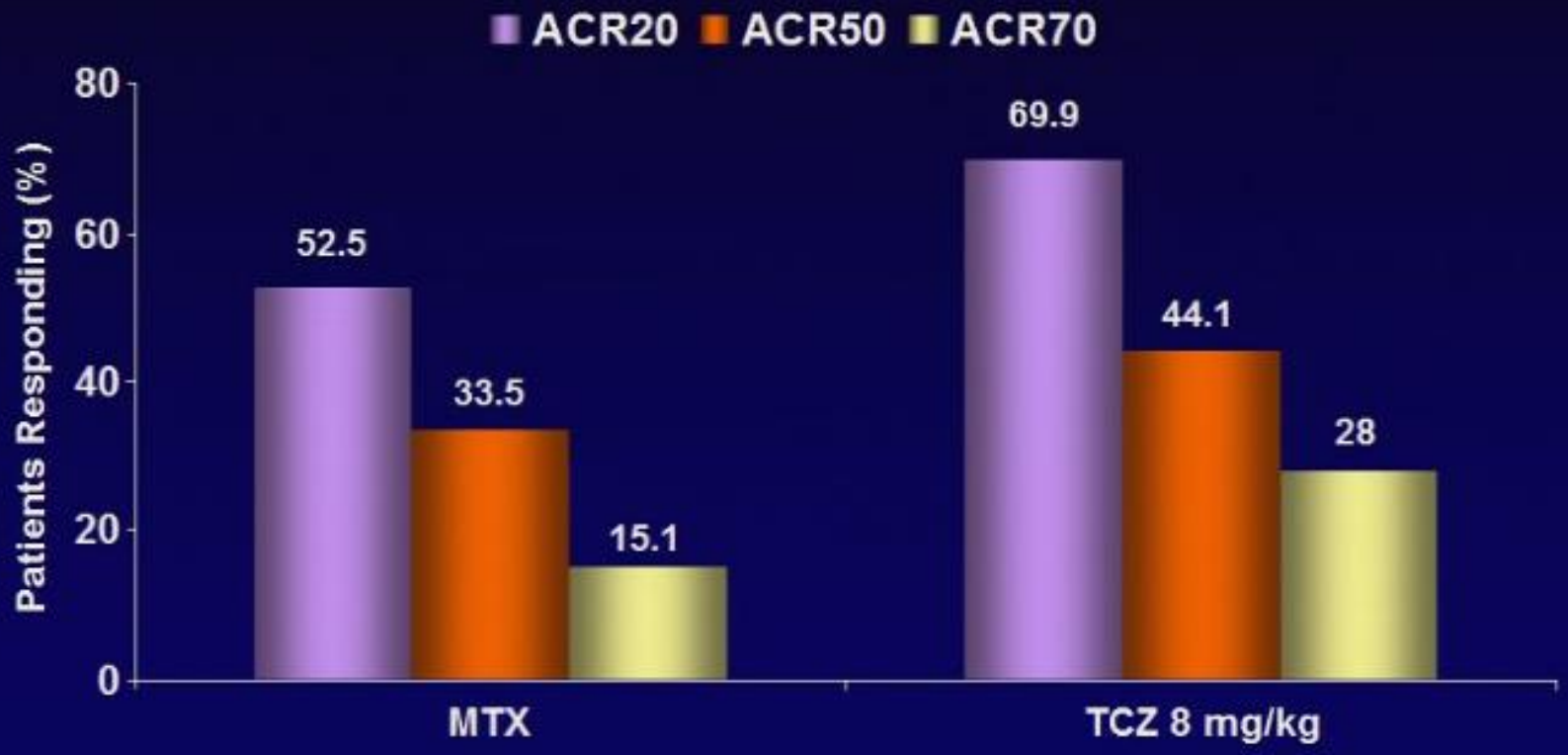
Adapted from Smolen and Steiner. *Nature Rev Drug Discovery*. 2003;2:473; Choy and Panayi. *N Engl J Med*. 2001;344:907; Silverman and Carson. *Arthritis Res Ther* 2003; 59(suppl 4):S1

Potential Roles of IL-6 in RA



Cronstein BN. *Bull NYU Hosp Jt Dis.* 2007;65:S11-S15.

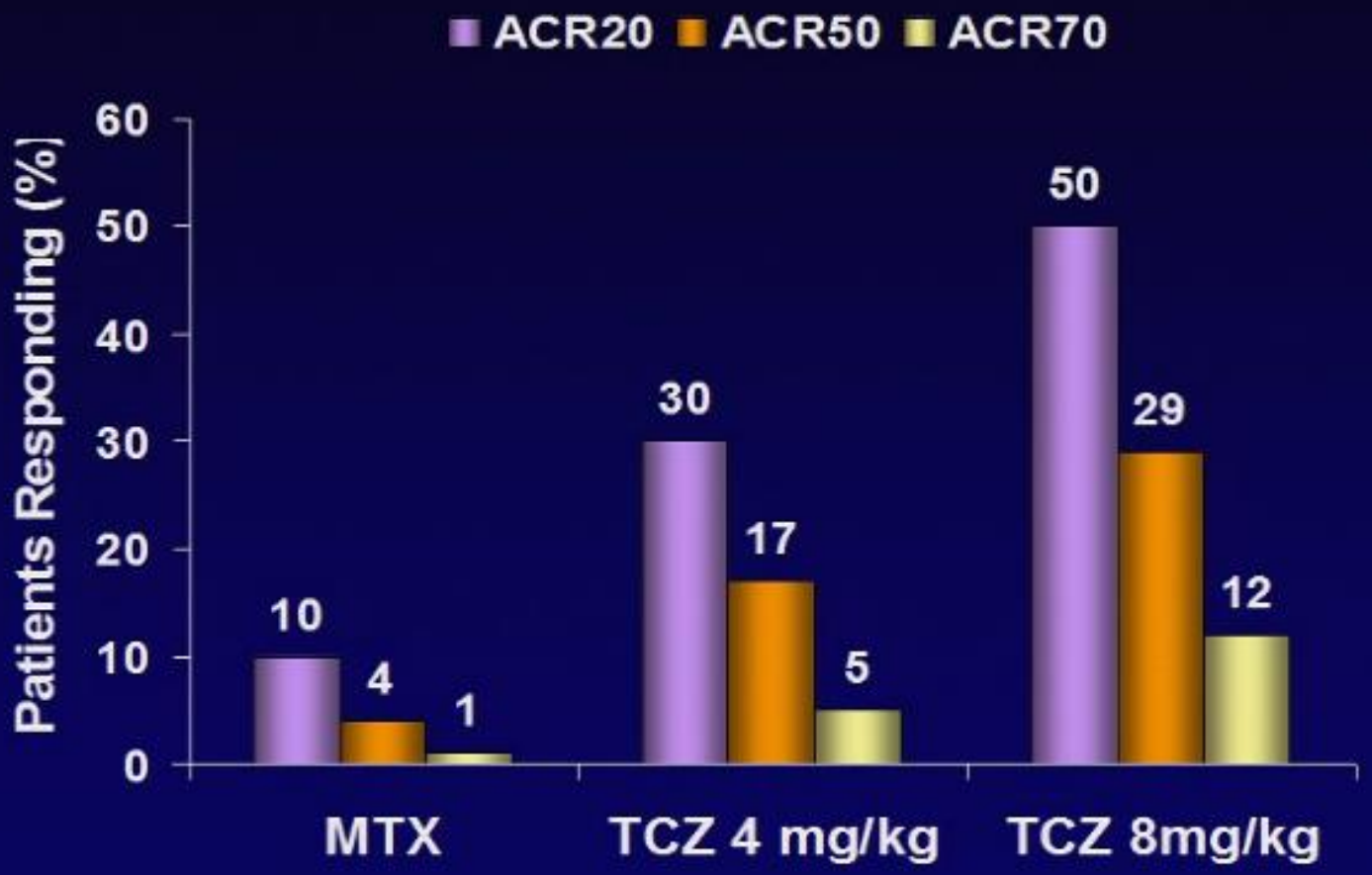
Tocilizumab MonoRx (MTX-Naïve) AMBITION



Jones G, Ann Rheum Dis 2010 69: 88-96

Tocilizumab is not FDA approved for the treatment of patiets with early RA

TNF Antagonist IRs: Tocilizumab (RADIATE)



Emery P et al. *Ann Rheum Dis*. 2008;67:1516-1523.

What this talk is about

- Looking beyond joints and impact on society

RA impacts work capacity

ARTHRITIS & RHEUMATISM
Vol. 52, No. 1, January 2005, pp 36–41
DOI 10.1002/art.20716

Early Suppression of Disease Activity Is Essential for Maintenance of Work Capacity in Patients With Recent-Onset Rheumatoid Arthritis

Five-Year Experience From the FIN-RACo Trial

Conclusion. **Prompt induction of remission translates into maintenance of work capacity. At 6 months, an ACR50 response is no better than an ACR20 response with regard to future productivity, while failure to achieve an ACR20 response carries a high risk for work disability.**

ARTHRITIS & RHEUMATISM
Vol. 48, No. 11, November 2003, pp 3046–3054
DOI 10.1002/art.11285

Association Between Etanercept Use and Employment Outcomes Among Patients With Rheumatoid Arthritis

Conclusion. **Among all persons who were employed at the time of RA diagnosis, having been in the etanercept clinical trials was associated with higher employment rates in 1999 and a greater number of hours per week of work in that year, suggesting that a randomized trial to establish the relationship between treatment and employment outcomes is now warranted.**

ARTHRITIS & RHEUMATISM
Vol. 54, No. 3, March 2006, pp 716–722
DOI 10.1002/art.21661

Infliximab Treatment Maintains Employability in Patients With Early Rheumatoid Arthritis

***Conclusion*. The actual employment rates among patients in the 2 treatment groups were not different. However, patients with early RA who were treated with MTX plus infliximab had a higher probability of maintaining their employability compared with those who were treated with MTX alone.**

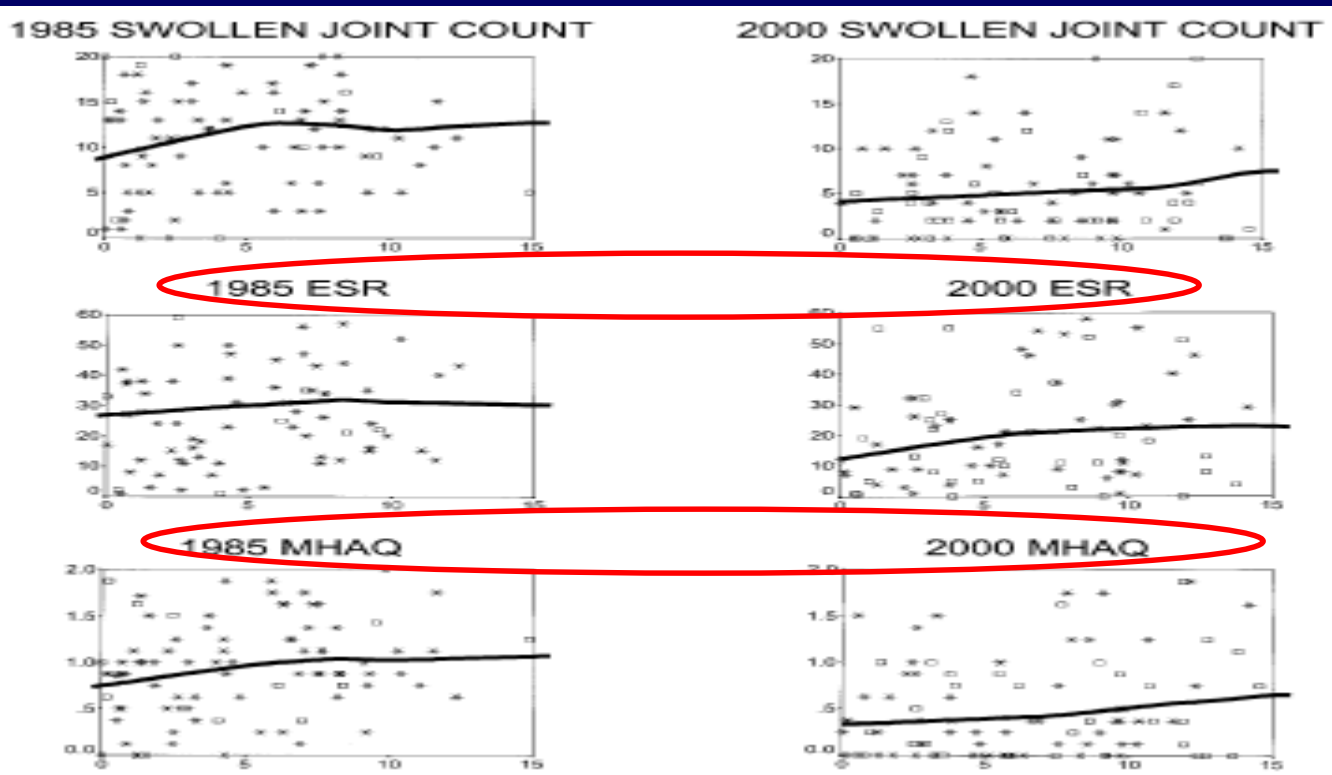
ARTHRITIS & RHEUMATISM
Vol. 52, No. 4, April 2005, pp 1009–1019
DOI 10.1002/art.20941

Patients Seen for Standard Rheumatoid Arthritis Care Have Significantly Better Articular, Radiographic, Laboratory, and Functional Status in 2000 Than in 1985

Conclusion. **Patients receiving standard care for RA in this setting had significantly better status, including radiographic scores, in 2000 than in 1985, associated with aggressive treatment strategies, prior to the introduction of biologic agents.**

Table 4. Twenty-eight–joint Disease Activity Scores (DAS28) in the 1985 cohort and the 2000 cohort*

DAS28	Disease activity level	1985 cohort, DAS28 without patient global status	2000 cohort	
			DAS28 without patient global status	DAS28 with global status
<2.6	Remission	3 (2.5)	14 (13.6)	14 (13.6)
2.6–3.19	Mild	5 (4.2)	12 (11.7)	15 (14.6)
3.2–5.09	Moderate	29 (24.4)	46 (44.7)	43 (41.7)
>5.1	Severe	82 (68.9)	31 (30.1)	31 (30.1)
Total		119 (100.0)	103 (100.0)	103 (100.0)



ARTHRITIS & RHEUMATISM
Vol. 48, No. 10, October 2003, pp 2750–2762
DOI 10.1002/art.11439

Direct Medical Costs and Their Predictors in Patients With Rheumatoid Arthritis

A Three-Year Study of 7,527 Patients

Results. **The mean total annual direct medical care cost in 2001 for a patient with RA was $9,519. Drug costs were $6,324 (66% of the total), while hospitalization costs were only $1,573 (17%). Approximately 25% of patients received biologic therapy. The mean total annual direct cost for patients receiving biologic agents was $19,016 per year, while the cost for those not receiving biologic therapy was $6,164. RA patients who were in the worst quartile of functional status, as measured by the Health Assessment Questionnaire,**

Direct Medical Costs and Their Predictors in Patients With Rheumatoid Arthritis

experienced direct medical costs for the subsequent year that were $5,022 more than the costs incurred by those in the best quartile. Physical status as determined by the Short Form 36 physical component scale had a similar large effect on RA costs, as did comorbidity. Medical insurance type played a more limited role. However, those without insurance had substantially lower service utilization and costs, and health maintenance organization patients had lower drug costs and total medical costs. Increased years of education, increased income, and majority ethnic status were all associated with increased drug costs but not hospitalization costs. Costs in all categories decreased after age 65 years.

RA impacts cardiovascular health

ARTHRITIS & RHEUMATISM
Vol. 56, No. 9, September 2007, pp 2905–2912
DOI 10.1002/art.22809

Reduction in the Incidence of Myocardial Infarction in Patients With Rheumatoid Arthritis Who Respond to Anti–Tumor Necrosis Factor α Therapy

Results From the British Society for Rheumatology Biologics Register

Conclusion. **These results indicate that RA patients treated with anti-TNFα do not have a lower incidence of MI compared with RA patients treated with traditional DMARDs. However, the risk of MI is markedly reduced in those who respond to anti-TNFα therapy by 6 months compared with nonresponders. This finding supports the notion that inflammation plays a pivotal role in MI.**

What this talk is about

- Weighing risk and benefits of treatment

ARTHRITIS & RHEUMATISM
Vol. 46, No. 9, September 2002, pp 2287–2293
DOI 10.1002/art.10524

Frequency of Infection in Patients With Rheumatoid Arthritis Compared With Controls

A Population-Based Study

Results. **The 609 RA patients and 609 non-RA infections, infections requiring hospitalization, and any documented infection in patients with RA were 1.70 (95% confidence interval [95% CI] 1.42–2.03), 1.83 (95% CI 1.52–2.21), and 1.45 (95% CI 1.29–1.64), respectively, after adjustment for age, sex, smoking status, leukopenia, corticosteroid use, and diabetes mellitus. Sites of infection with the highest risk ratios were bone, joints, skin, soft tissues, and the respiratory tract.**

ARTHRITIS & RHEUMATISM
Vol. 46, No. 9, September 2002, pp 2294–2300
DOI 10.1002/art.10529

Predictors of Infection in Rheumatoid Arthritis

Increasing age, presence of extraarticular manifestations of RA, leukopenia, and comorbidities (chronic lung disease, alcoholism, organic brain disease, and diabetes mellitus), as well as use of corticosteroids, were strong predictors of infection ($P < 0.004$) in both univariate and multivariate analyses. Notably, use of disease-modifying antirheumatic drugs was not associated with increased risk of infection in multivariate analyses, after adjustment for demographic characteristics, comorbidities, and disease-related variables.

ARTHRITIS & RHEUMATISM
Vol. 54, No. 8, August 2006, pp 2368–2376
DOI 10.1002/art.21978

Rates of Serious Infection, Including Site-Specific and Bacterial Intracellular Infection, in Rheumatoid Arthritis Patients Receiving Anti–Tumor Necrosis Factor Therapy

Results From the British Society for Rheumatology Biologics Register

Conclusion. **In patients with active RA, anti-TNF therapy was not associated with increased risk of overall serious infection compared with DMARD treatment, after adjustment for baseline risk. In contrast, the rate of serious skin and soft tissue infections was increased, suggesting an important physiologic role of TNF in host defense in the skin and soft tissues beyond that in other tissues.**

ARTHRITIS & RHEUMATISM
Vol. 56, No. 6, June 2007, pp 1754–1764
DOI 10.1002/art.22600

Anti–Tumor Necrosis Factor α Therapy and the Risk of Serious Bacterial Infections in Elderly Patients With Rheumatoid Arthritis

Conclusion. **In a large cohort of patients with RA, we found no increase in serious bacterial infections among users of anti-TNFα therapy compared with users of MTX. Glucocorticoid use was associated with a dose-dependent increase in such infections.**

ARTHRITIS & RHEUMATISM
Vol. 54, No. 2, February 2006, pp 628–634
DOI 10.1002/art.21568

Treatment for Rheumatoid Arthritis and the Risk of Hospitalization for Pneumonia

Associations With Prednisone, Disease-Modifying Antirheumatic Drugs, and Anti–Tumor Necrosis Factor Therapy

Results. After adjustment for covariates, prednisone use increased the risk of pneumonia hospitalization (hazard ratio [HR] 1.7 [95% confidence interval 1.5–2.0]), including a dose-related increase in risk (≤5mg/day HR 1.4 [95% confidence interval 1.1–1.6], >5–10 mg/day HR 2.1 [95% confidence interval 1.7–2.7], >10 mg/day HR 2.3 [95% confidence interval 1.6–3.2]). Leflunomide also increased the risk (HR 1.2 [95% confidence interval 1.0–1.5]). HRs for etanercept (0.8 [95% confidence interval 0.6–110]) and sulfasalazine (0.7 [95% confidence interval 0.5–1.0]) did not reflect an increased risk of pneumonia. HRs for infliximab, adalimumab, and methotrexate were not significantly different from zero.

Conclusion. There is a dose-related relationship between prednisone use and pneumonia risk in RA. No increase in risk was found for anti–tumor necrosis factor therapy or methotrexate. These data call into question the belief that low-dose prednisone is safe. Because corticosteroid use is common in RA, the results of this study suggest that prednisone exposure may have important public health consequences.

ARTHRITIS & RHEUMATISM
Vol. 56, No. 9, September 2007, pp 2896–2904
DOI 10.1002/art.22808

Serious Infection Following Anti–Tumor Necrosis Factor α Therapy in Patients With Rheumatoid Arthritis

Lessons From Interpreting Data From Observational Studies

Results. **When the at-risk period was defined as "receiving treatment", the adjusted incidence rate ratio comparing patients receiving anti-TNFα therapy with patients receiving DMARD therapy was 1.22 (95% confidence interval [95% CI] 0.88–1.69). Limiting followup to the first 90 days, however, revealed an adjusted incidence rate ratio of 4.6 (95% CI 1.8–11.9). Rates of infection were increased in the 90 days immediately following drug discontinuation and beyond, explained by selection factors for drug discontinuation.**

ARTHRITIS & RHEUMATISM
Vol. 52, No. 6, June 2005, pp 1766–1772
DOI 10.1002/art.21043

Effectiveness of Recommendations to Prevent Reactivation of Latent Tuberculosis Infection in Patients Treated With Tumor Necrosis Factor Antagonists

Results. **Active TB developed in 34 patients, of whom 32 started taking TNF antagonists prior to the official recommendations on latent TB infection (pre-OR) and 2 began treatment after the recommendations**

Conclusion. **Strategies to treat latent TB infection that are tailored to the at-risk population can effectively and safely lessen the likelihood of active TB in patients treated with TNF antagonists.**

ARTHRITIS & RHEUMATISM
Vol. 50, No. 6, June 2004, pp 1740–1751
DOI 10.1002/art.20311

Lymphoma in Rheumatoid Arthritis

The Effect of Methotrexate and Anti–Tumor Necrosis Factor Therapy in 18,572 Patients

Lymphoma was associated with increasing age, male sex, and education.

Conclusion. **Lymphomas are increased in RA. Although the SIR is greatest for anti-TNF therapies, differences between therapies are slight, and confidence intervals for treatment groups overlap. The increased lymphoma rates observed with anti-TNF therapy may reflect channeling bias, whereby patients with the highest risk of lymphoma preferentially receive anti-TNF therapy. Current data are insufficient to establish a causal relationship between RA treatments and the development of lymphoma.**

ARTHRITIS & RHEUMATISM
Vol. 56, No. 5, May 2007, pp 1433–1439
DOI 10.1002/art.22579

The Effect of Methotrexate and Anti–Tumor Necrosis Factor Therapy on the Risk of Lymphoma in Rheumatoid Arthritis in 19,562 Patients During 89,710 Person-Years of Observation

Results. Of the 19,591 participants, 55.3% received biologic agents and 68.0% received MTX while enrolled in the NDB. The lymphoma incidence rate was 105.9 (95% confidence interval [95% CI] 86.6–129.5) per 100,000 person-years of exposure. Compared with the SEER (Surveillance, Epidemiology, and End-Results) lymphoma database, the standardized incidence ratio was 1.8 (95% CI 1.5–2.2). The odds ratio (OR) for lymphoma in patients who received anti-TNF therapy compared with patients who did not receive anti-TNF therapy was 1.0 (95% CI 0.6–1.8 [$P = 0.875$]). The OR for lymphoma in patients who received anti-TNF plus MTX therapy compared with patients who received MTX treatment alone was 1.1 (95% CI 0.6–2.0 [$P = 0.710$]). Infliximab and etanercept considered individually also were not associated with a risk of lymphoma.

Conclusion. In a study of lymphoma in 19,591 RA patients over 89,710 person-years of followup, which included exposure to anti-TNF therapy in 10,815 patients, we did not observe evidence for an increase in the incidence of lymphoma among patients who received anti-TNF therapy.

ARTHRITIS & RHEUMATISM
Vol. 44, No. 12, December 2001, pp 2862–2869

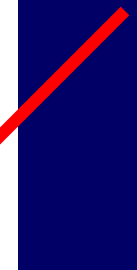
Published by Wiley-Liss, Inc.

Demyelination Occurring During Anti–Tumor Necrosis Factor α Therapy for Inflammatory Arthritides

Results. **Nineteen patients with similar neurologic events were identified from the FDA database, 17 following etanercept administration and 2 following infliximab administration for inflammatory arthritis. All neurologic events were temporally related to anti-TNFα therapy, with partial or complete resolution on discontinuation. One patient exhibited a positive rechallenge phenomenon.**

Conclusion. **Further surveillance and studies are required to better define risk factors for and frequency of adverse events and their relationship to anti-TNFα therapies. Until more long-term safety data are available, consideration should be given to avoiding anti-TNFα therapy in patients with preexisting multiple sclerosis and to discontinuing anti-TNFα therapy im-**

mediately when new neurologic signs and symptoms occur, pending an appropriate evaluation.



ARTHRITIS & RHEUMATISM
Vol. 50, No. 6, June 2004, pp 1959–1966
DOI 10.1002/art.20454

Increased Risk of Coccidioidomycosis in Patients Treated With Tumor Necrosis Factor α Antagonists

Results. **Thirteen cases of documented coccidioidomycosis were associated with TNFα antagonist therapy. Twelve cases were associated with the use of infliximab and 1 case with etanercept. Among the cohort of patients from a single medical center, 7 of the 247 patients receiving infliximab and 4 of the 738 patients receiving other therapies developed symptomatic coccidioidomycosis (relative risk 5.23, 95% confidence interval 1.54–17.71; $P < 0.01$).**

Conclusion. **Patients with inflammatory arthritis who are undergoing treatment with infliximab appear to be at higher risk for developing symptomatic coccidioidomycosis as compared with those not receiving infliximab.**

ARTHRITIS & RHEUMATISM
Vol. 58, No. 10, October 2008, pp 2949–2957
DOI 10.1002/art.23883

REVIEW

Viral Infection and Reactivation in Autoimmune Disease

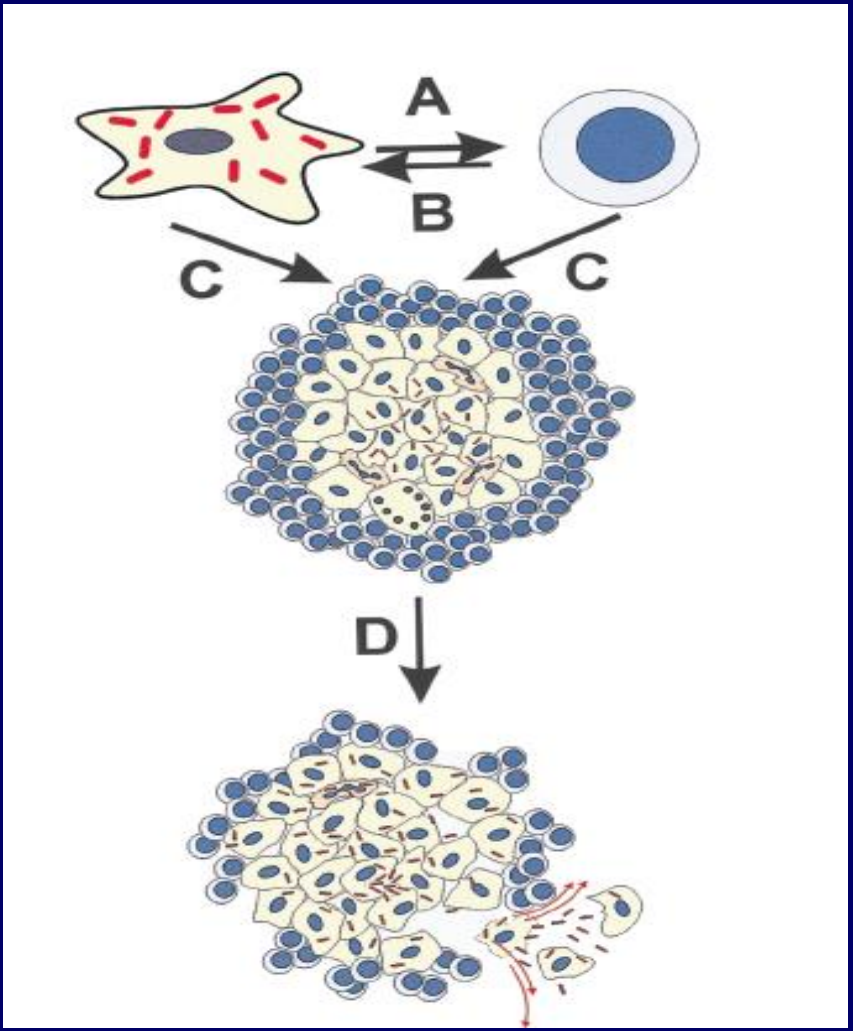
Table 2. Case reports of reactivation of hepatitis B virus (HBV) in autoimmune disease

Treatment, author, year (ref.)	Diagnosis	Treatment	Outcome
Biologic therapy			
Ostuni et al, 2003 (39)	RA*	Infliximab, methotrexate, prednisone	Infliximab and methotrexate stopped; successfully treated with lamivudine
Wendling et al, 2005 (40)	Spondylarthritis	Infliximab	Successfully treated with lamivudine
Esteve et al, 2004 (34)	Crohn's disease	Azathioprine, infliximab†	1 recovered, 1 died
Madonia et al, 2007 (38)	Crohn's disease	Infliximab, prednisone	Successfully treated with lamivudine
Millonig et al, 2006 (82)	Crohn's disease	Infliximab	Successfully treated with lamivudine
Nonbiologic therapy			
Flowers, 1990 (83)	RA	Methotrexate†	Liver transplant
Hagiyama et al, 2004 (84)	RA	Methotrexate	Died
Ito et al, 2001 (85)	RA	Methotrexate, prednisolone†	Died
Narvaez et al, 1998 (86)	RA	Methotrexate†	Died
Nakanishi et al, 1998 (87)	Polymyositis	Prednisolone	Treatment with interferon alfa and cyclosporin A progressively reduced transaminase and HBV DNA levels, leading to recovery

What this talk is about

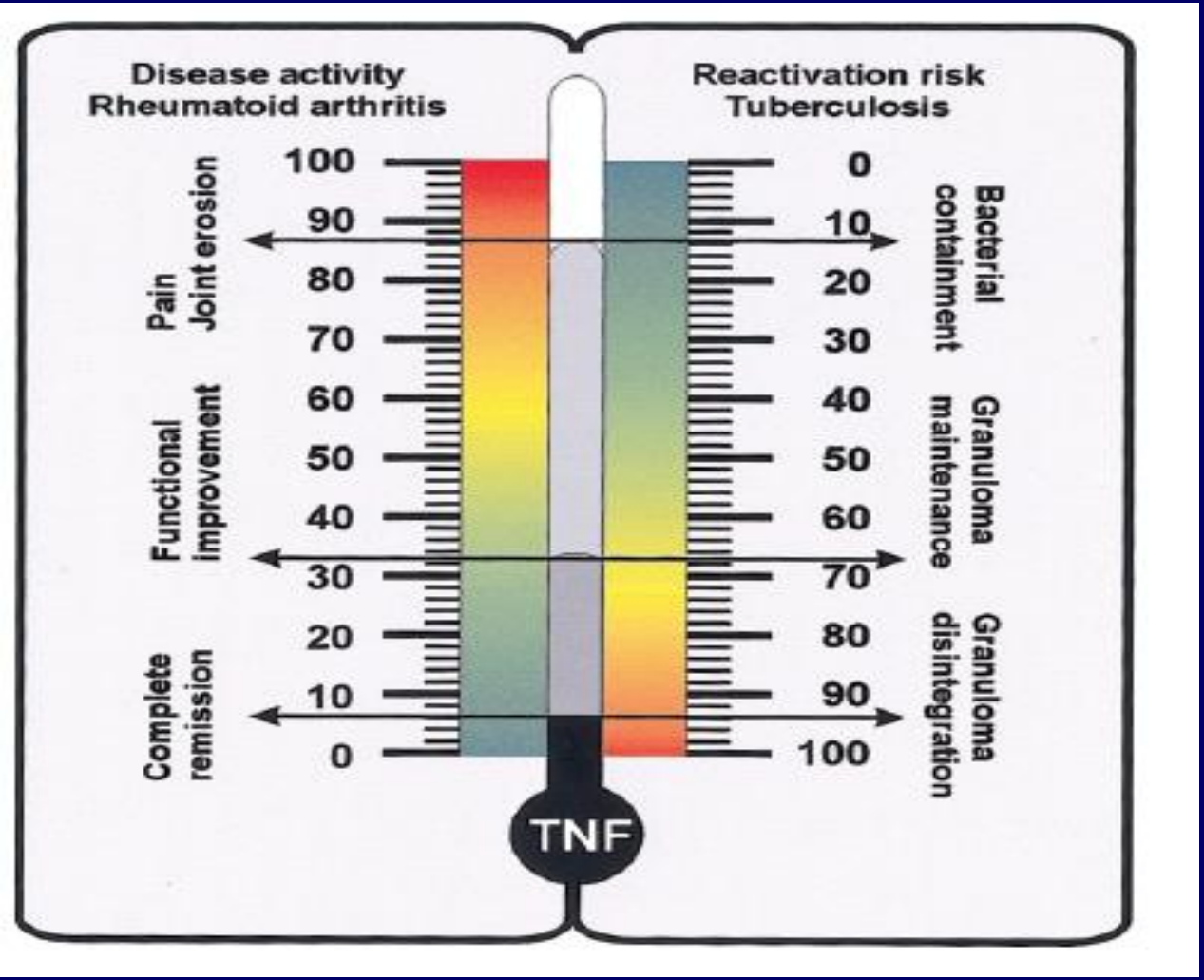
- Surveillance of co morbidities

Role of TNF in controlling infection



- CID 2005:41 (Suppl 3) • Ehlers

"TNF-o-meter"
Finding the right balance



List of recommended vaccines

Vaccine	Routine (not immumocompromised)	Human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome	Severely immunocompromised (non-HIV related)†	Post–solid organ transplant or chronic immunosuppresive therapy
Hepatitis B	Use if indicated	Use if indicated	Use if indicated	Use if indicated
Hib	Not recommended	Consider§	Recommended	Recommended
Influenza (inactivatec	Recommended if ≥50 y of age	Recommended	Recommended	Recommended
Influenza (LAIV)	Use if indicated	Contraindicated	Contraindicated	Contraindicated
MMR (MR/M/R)	Use if indicated	Recommended/consider‖	Contraindicated	Contraindicated
Meningococcal	Use if indicated	Use if indicated	Use if indicated	Use if indicated
Pneumococcal (PPV)	Recommended if ≥65 y of age	Recommended	Recommended	Recommended
Td	Recommended	Recommended	Recommended	Recommended
Varicella	Use if indicated	Contraindicated	See note¶	Contraindicated

List of Contraindicated vaccines

Vaccine	No immunocompromised	Human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome	Severely immunocompromised (non-HIV related)†	Post–solid organ transplant or chronic immunosuppressive therapy
Live vaccines				
BCG	Use if indicated	Contraindicated	Contraindicated	Contraindicated
Typhoid, Ty21a	Use if indicated	Contraindicated	Contraindicated	Contraindicated
Vaccinia	Use if indicated	Contraindicated	Contraindicated	Contraindicated
Varicella (adults)	Use if indicated	Contraindicated	See note‡	Contraindicated§
Yellow fever‖	Use if indicated	Contraindicated	Contraindicated	Contraindicated
Killed (inactivated) vaccines				
Anthrax	Use if indicated	Use if indicated	Use if indicated	Use if indicated
Polio (IPV)	Use if indicated	Use if indicated	Use if indicated	Use if indicated
Rabies	Use if indicated	Use if indicated	Use if indicated	Use if indicated
Typhoid, inactivated	Use if indicated	Use if indicated	Use if indicated	Use if indicated

Summary

- Early diagnosis and treatment
- Aggressive monitoring to prevent joint damage
- Aim for maintenance of remission and functional capacity
- Surveillance of infections and comorbidites