Update in Rheumatoid Arthritis

Sandeep K. Agarwal M.D., Ph.D.

Chief, Immunology Allergy and Rheumatology

Department of Medicine

The Cullen Trust for Health Care Endowed Chair in Immunology

Director, Biology of Inflammation Center

Baylor College of Medicine

MARGARET M. & ALBERT B. ALKEK DEPARTMENT OF MEDICINE

IMMUNOLOGY, ALLERGY AND RHEUMATOLOGY

BIOLOGY OF INFLAMMATION CENTER · BAYLOR COLLEGE OF MEDICINE ·

Biology of Inflammation Center

Disclosures

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New Yorker, July 2008

OBJECTIVES

1. Discuss updates in the pathogenesis of rheumatoid arthritis

2. Discuss the clinical presentation and assessment of patients with rheumatoid arthritis

3. Discuss updates in the treatment of rheumatoid arthritis

"When an arthritis patient walks in the front door, I feel like leaving by the back door"
-Sir William Osler

Corticosteroids
Nonsteroidals

Synthetic DMARDS
Hydroxychloroquine
Sulfasalazine
Methotrexate
Leflunomide

Biologics
TNF inhibitors (etanercept, infliximab, adalimumab, golimumab, certolizumab)
IL1ra (anakinra)
AntiCD20 mAb (rituximab)
CTLA4Ig (abatacept)
AntiIL6R (tocilizumab, sarlimumab)

Targeted synthetics
Tofacitinib
Baracitinib
Upadacitinib

Rheumatoid Arthritis : Epidemiology

- Systemic progressive inflammatory disorder
- Predominantly manifests in the synovial membrane of diarthroidal joints but can also have extrarticular manifestations
  - Classically presents as a symmetric small joint polyarthritis
- Prevalence of 0.8% in most developed countries
- Female : Male ratio of 2.5 : 1
- Peak incidence is 4^{th} to 6^{th} decades of life
- 2013 health care costs $10 billion
  - Societal cost $45 billion

Evidence for genetics (RA)

unrelated individuals

risk

0.5-1%

first-degree relatives

3-5%

identical twins (triplets!)

15%

Suggest 50-60% of risk is genetic

Slide courtesy of Robert Plenge MDPHD, Harvard Medical School

Rheumatoid arthritis : risk factors

GENETIC

–MHC Class II

- DR4 : HLA-DRB1*0401 and HLA-DRB1*0404
- DR1 : HLA-DRB1*0101
- Shared epitope : QKRAA or QRRAA on DRβ chain

–Other genetic factors - Single nucleotide polymorphisms

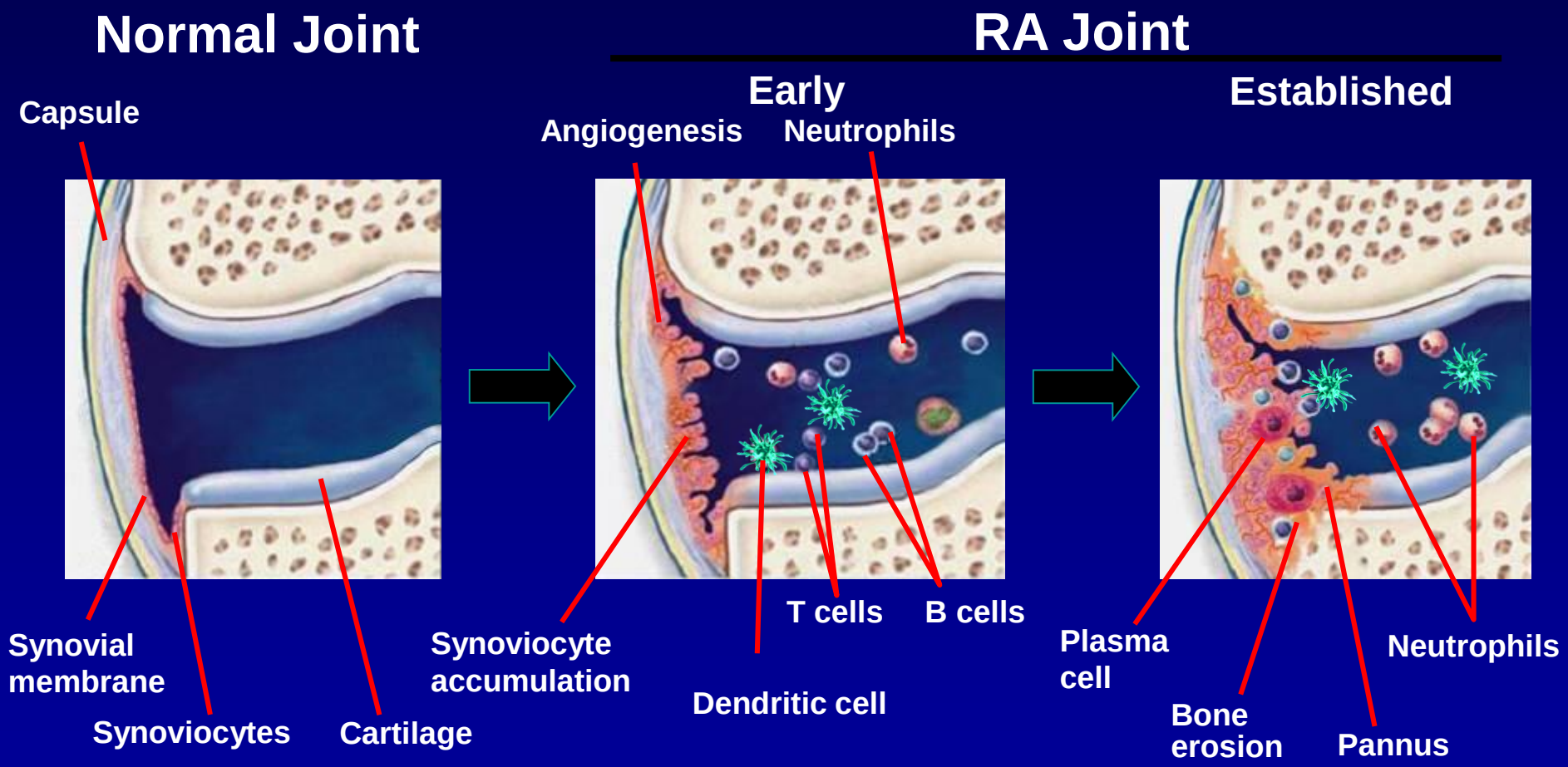
- PTPN22, STAT4, Tyk2, CD40, TRAF-C1 locus, CTLA4, CD28
- PADI-4 (peptidylarginine deiminase)
- And the list continues to grow2014 – 101 confirmed RA risk loci in individuals of European and Asian Ancestry (Nature 2013)

- But not ready for clinical application yet

ENVORINMENTAL

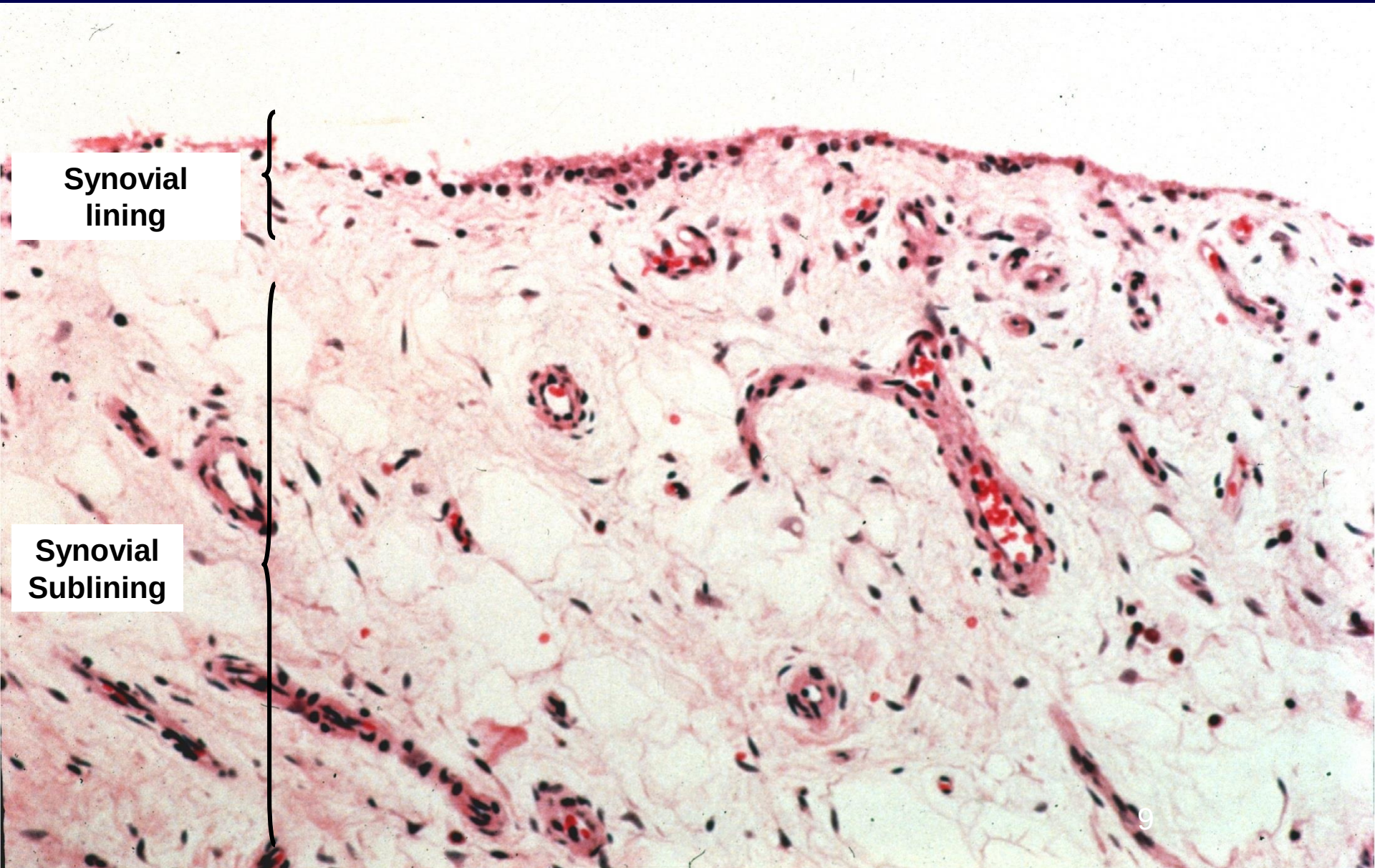
–Smoking – may have a role in the process of citrullination in RA

Pathophysiology of RA



Adapted from Choy EH et al. *N Engl J Med.* 2001;344:907-916.

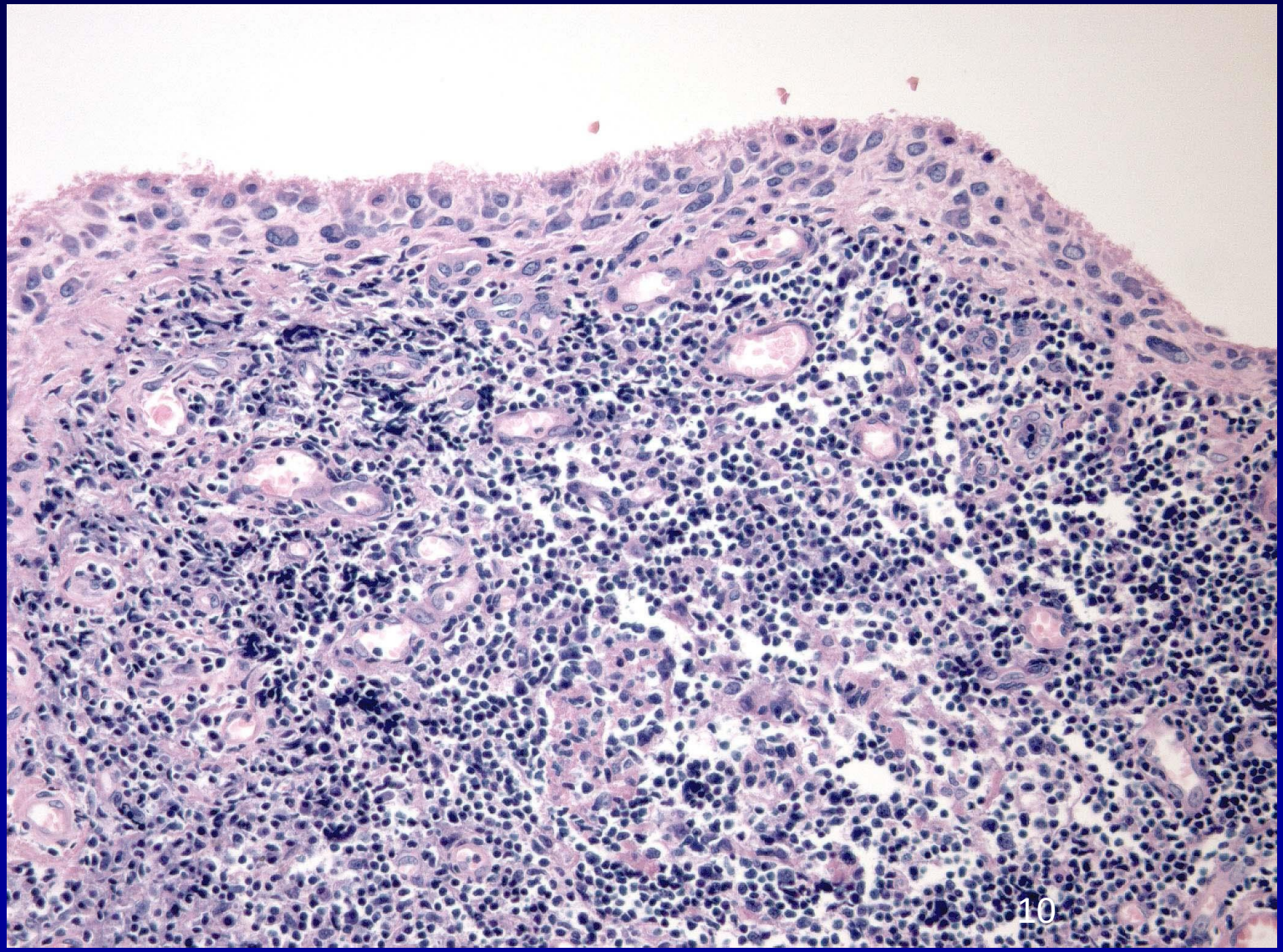
Normal Synovium



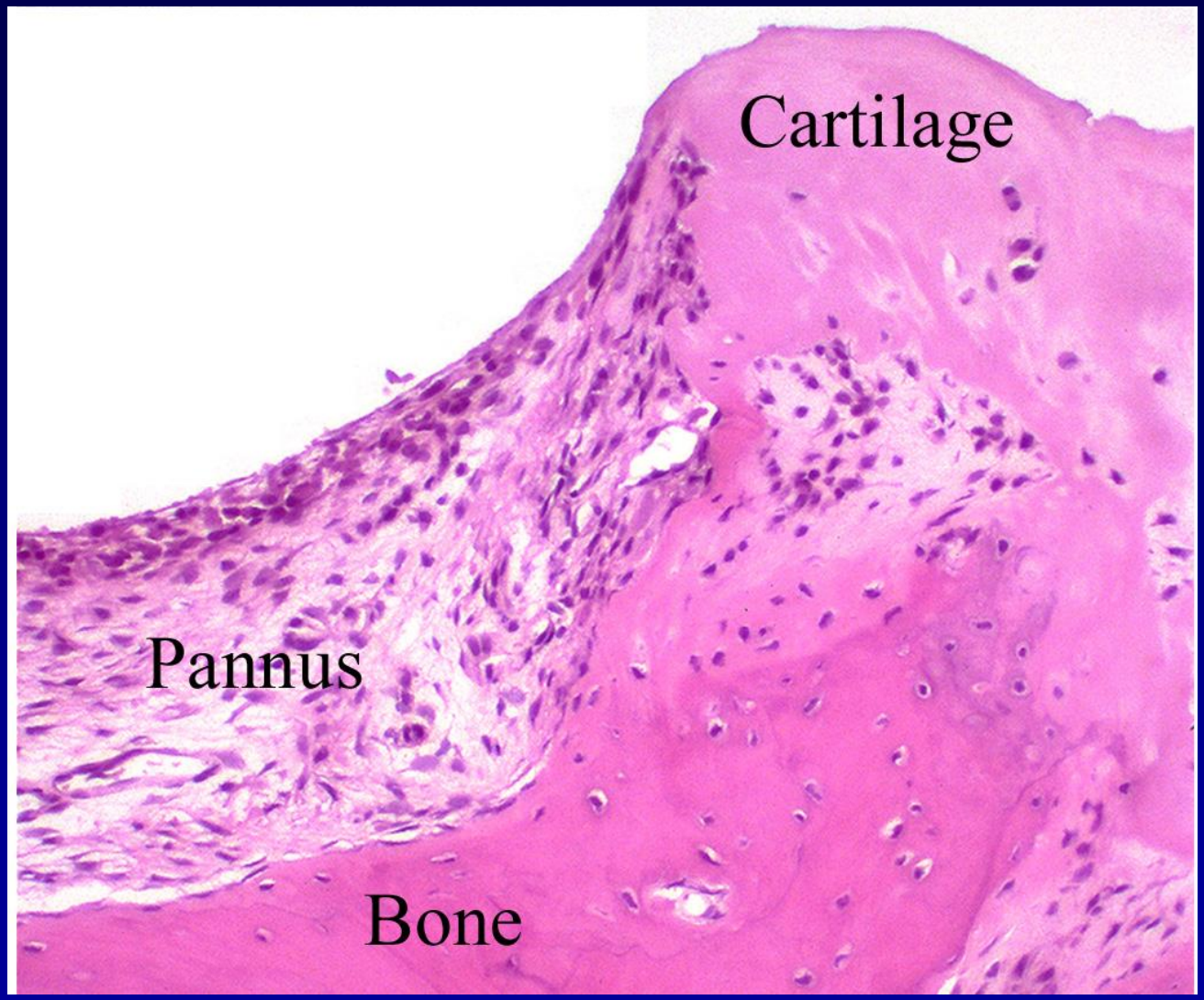
Rheumatoid Arthritis Synovial Membrane

Hyperplastic synovial lining

Inflamed Synovial Sublining



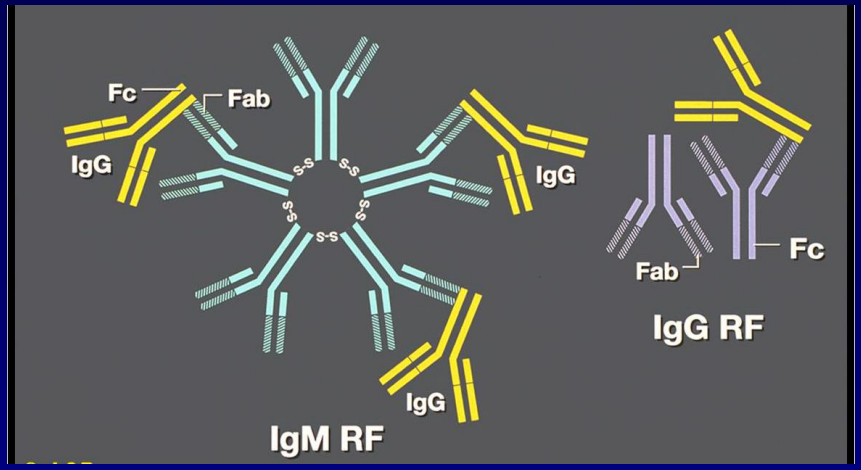
Rheumatoid Arthritis: Pannus



Lee, DM and Weinblatt, ME 2001. Lancet 358:903

Rheumatoid Factor

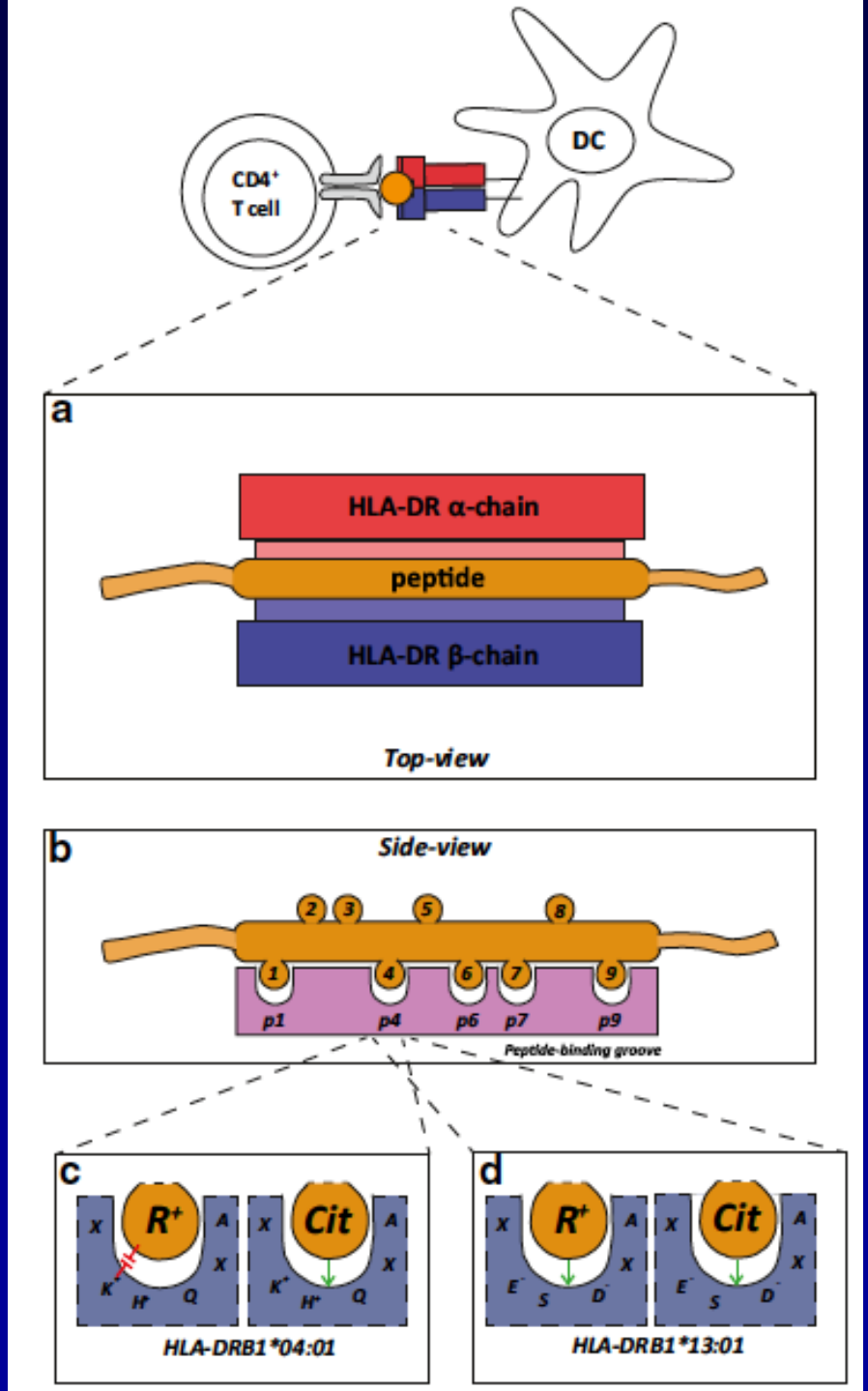
- Antibodies against the Fc portion of IgG
- Sensitivity for RA : 60-70%
- Specificity for RA : 70-80%
- Also found in
  - Other autoimmune disease
  - Healthy people (5%)
    - 3-25% of elderly
  - Bacterial endocarditis
  - Hepatitis B or C
  - Tuberculosis
  - Syphilis
  - Malignancies



Anti-Citrullinated peptide antibodies

- Citrulline is a non-standard amino acid, created by de-imination of arginine residues
  - Peptidylarginine deiminase (PADI)
- First were identified as anti-perinuclear factor (APF) or anti-filaggrin antibodies (AFA) or anti-keratin antibodies (AKA)
- Anti-cyclic citrullinated peptide antibodies (aCCP)
  - Sensitivity for RA : 50-75%
  - Specificity for RA : 90-95%
- Can be detected 1.5-9 years prior to the dx of RA (as can RF)

HLA variants and peptide binding: Effect of citrullination



Immunogenetics (2017) 69:597–603

RA : CLINICAL

Rheumatoid Arthritis : Clinical Features

- **Symptoms**
  - Pain
  - Stiffness
    - Prolonged AM stiffness > 1 hr
  - Swelling
  - Weakness
  - Deformity
  - Fatigue
  - Malaise
- **Physical Examination**
  - Tenderness to palpation
  - Synovial thickening
  - Joint effusions
  - Erythema
  - Decreased Range of Motion
  - Subluxation
- **Distribution**
  - Symmetric
  - Distal joints more than proximal
  - PIP, MCP, MTP, wrist, ankle > elbow, knee, shoulder, hip

Structural joint abnormality vs. Synovitis

	STRUCTURAL	SYNOVITIS
SUBJECTIVE	Symptoms with use	Symptoms with use and rest
	Minimal AM stiffness	Prominent AM stiffness
	Gradual worsening course	Course may fluctuate
	No acute exacerbation	Flares common
	No systemic symptoms	Systemic symptoms common
OBJECTIVE	Primarily weight bearing joints and fingers	Weight bearing joints, fingers and affect wrists, elbows, shoulders
	Crepitance and bony hypertrophy	Soft tissue swelling
	X-rays usually positive	X-rays negative early (MRI better at early)
	Cartilage loss localized, new bone growth	Cartilage loss diffuse, erosions

Lab Evaluation of Systemic Rheumatic Disease

- Lytes, BUN, Cr
- CBC w diff
- Urinalysis
- ESR, CRP

- Rheumatoid factor
- Anti-CCP antibodies
- ANA by immunofluorescence
  - Other autoAb if positive

- Hepatitis B and C serology
- TSH
- Xrays of hands and feet
  - And/or affected joints

- If history indicates:
  - Lyme serology
  - Parvovirus serology
  - Uric Acid
  - HLA B27

- Arthrocentesis

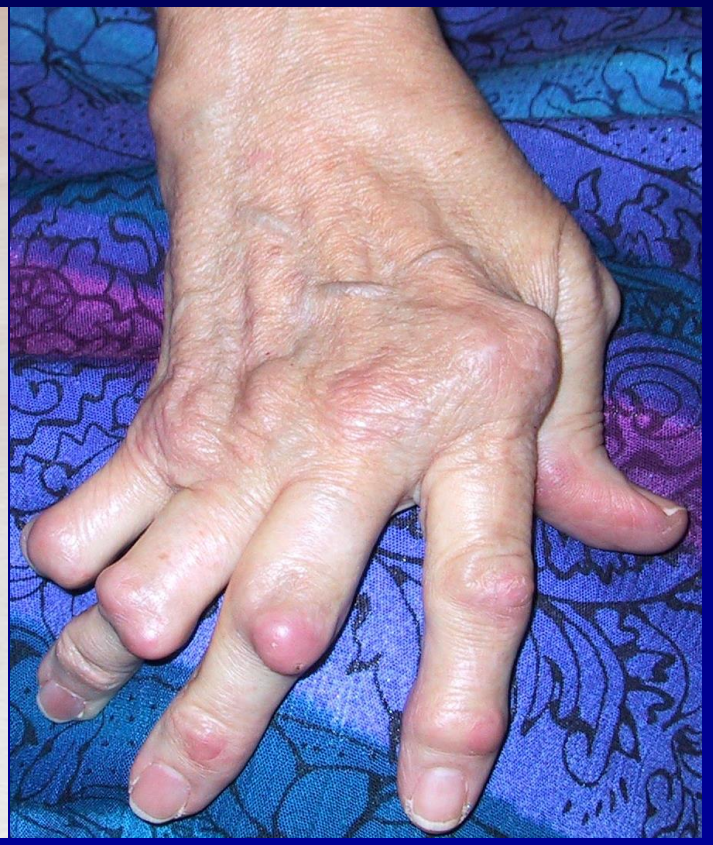
RA – Natural History

- Clinical Course
  - 10% may remit within 3-6 months
  - 60-70% variable sine wave course with overall progressive worsening
  - 10-20% relentless progression
- 70% have erosive changes detectable by Xrays by 2 years (MRI earlier)
- After 20 years, 60% of patients will have significant functional disability
- Increased incidence of
  - Infections
  - Cardiovascular disease
  - Lymphoma
- Decreased Life Expectancy
  - Standardized mortality rate of 1.70
  - Men live 7 years less
  - Women live 3 years less

Rheumatoid Arthritis : clinical images

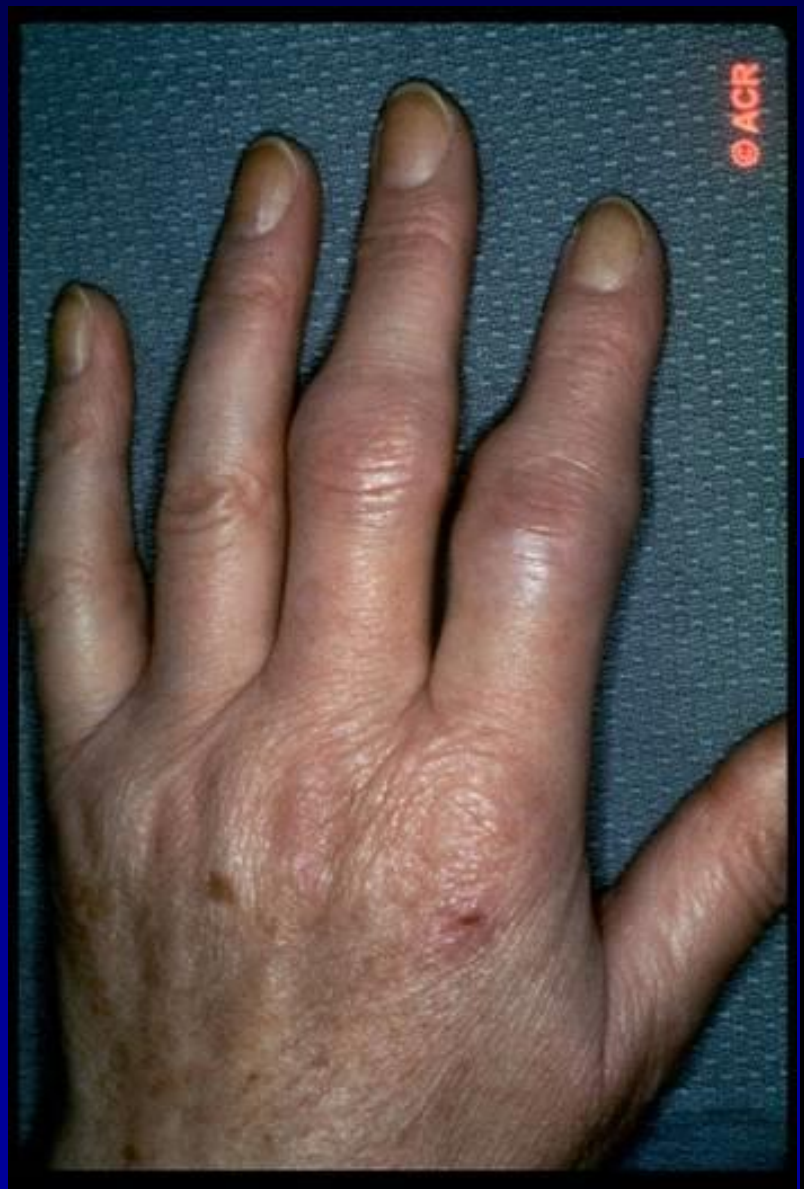
Early RA **Intermediate RA** **Severe RA**

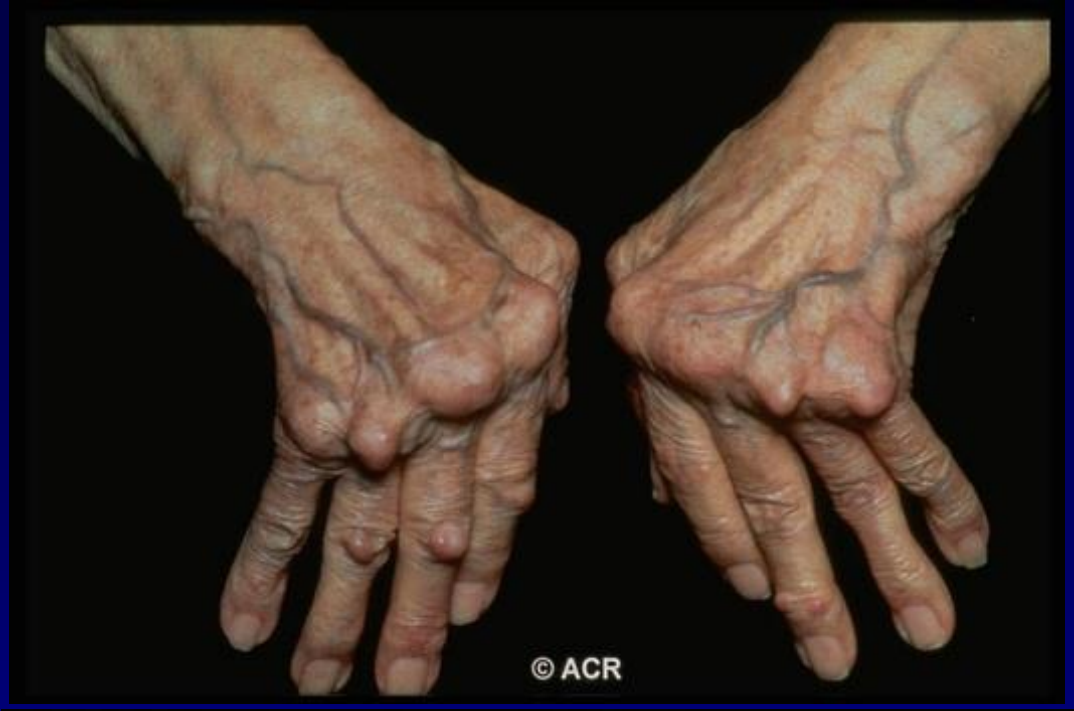


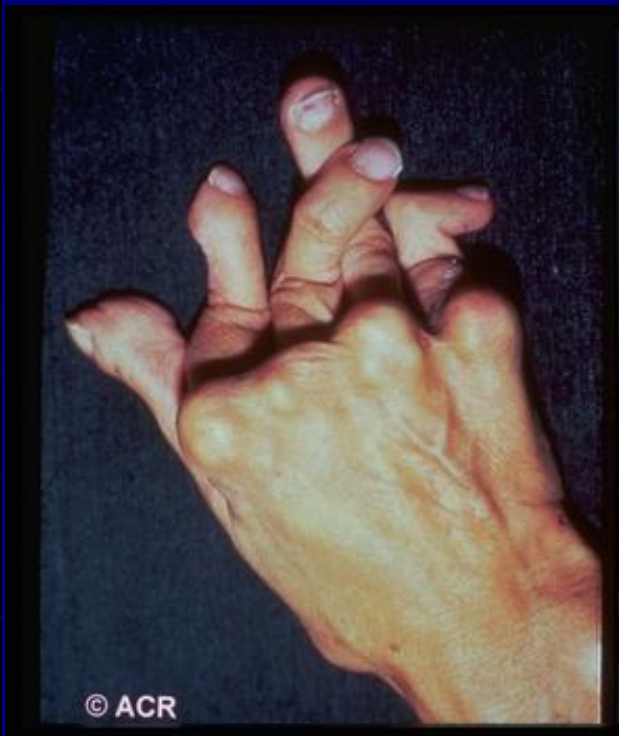


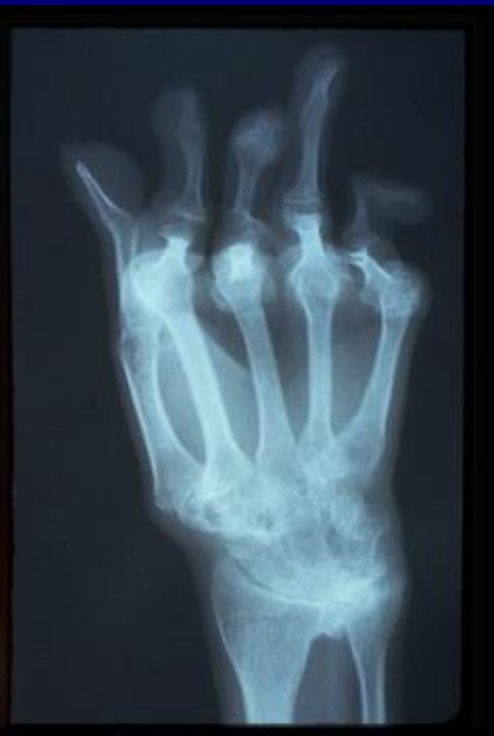
Courtesy of J. Cush, 2002.

Rheumatoid Arthritis



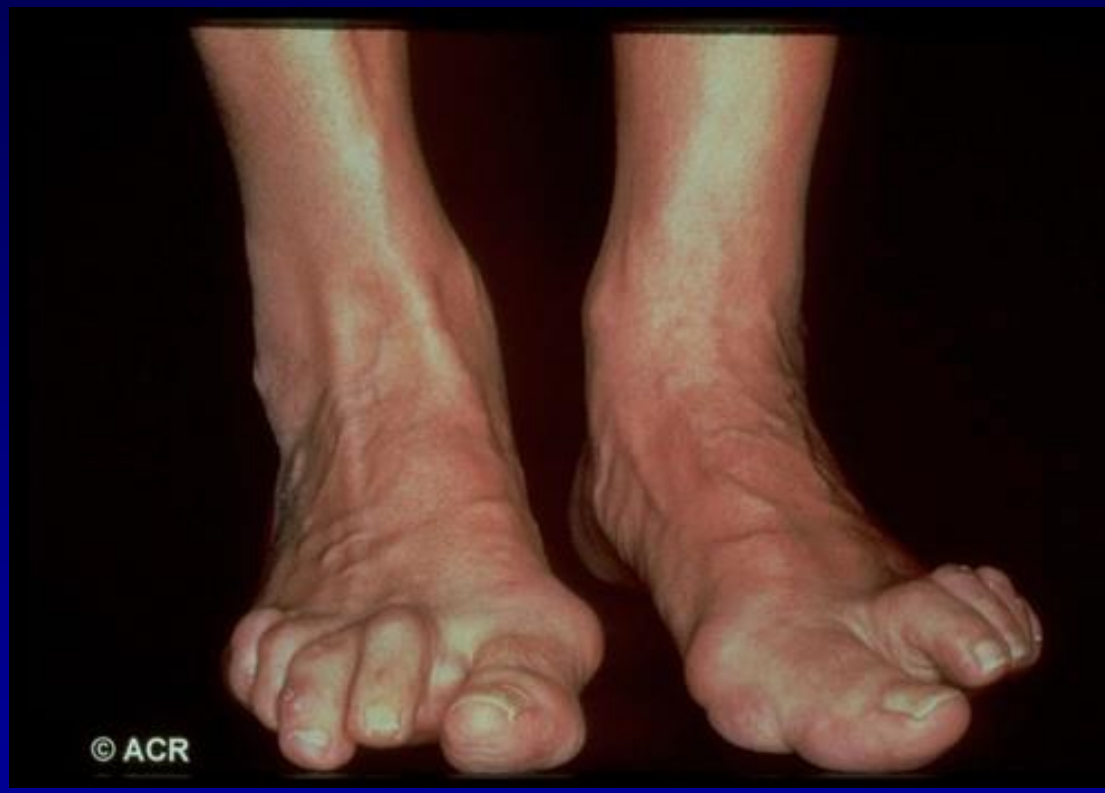




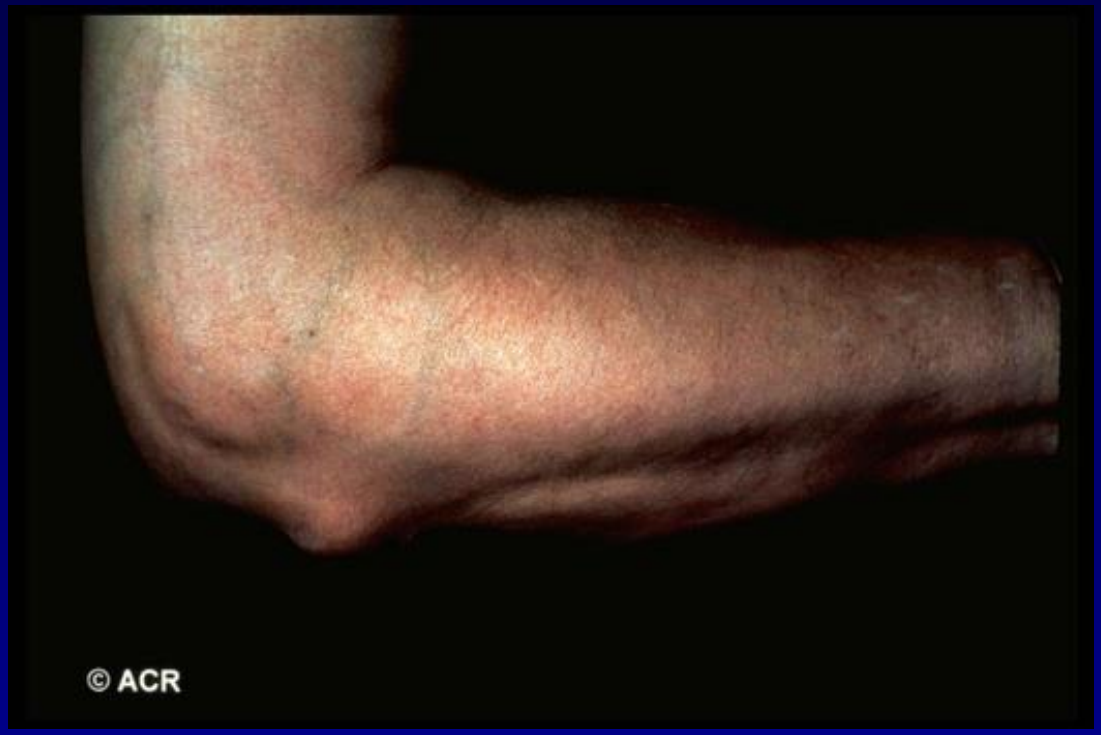


Rheumatoid Arthritis : clinical images

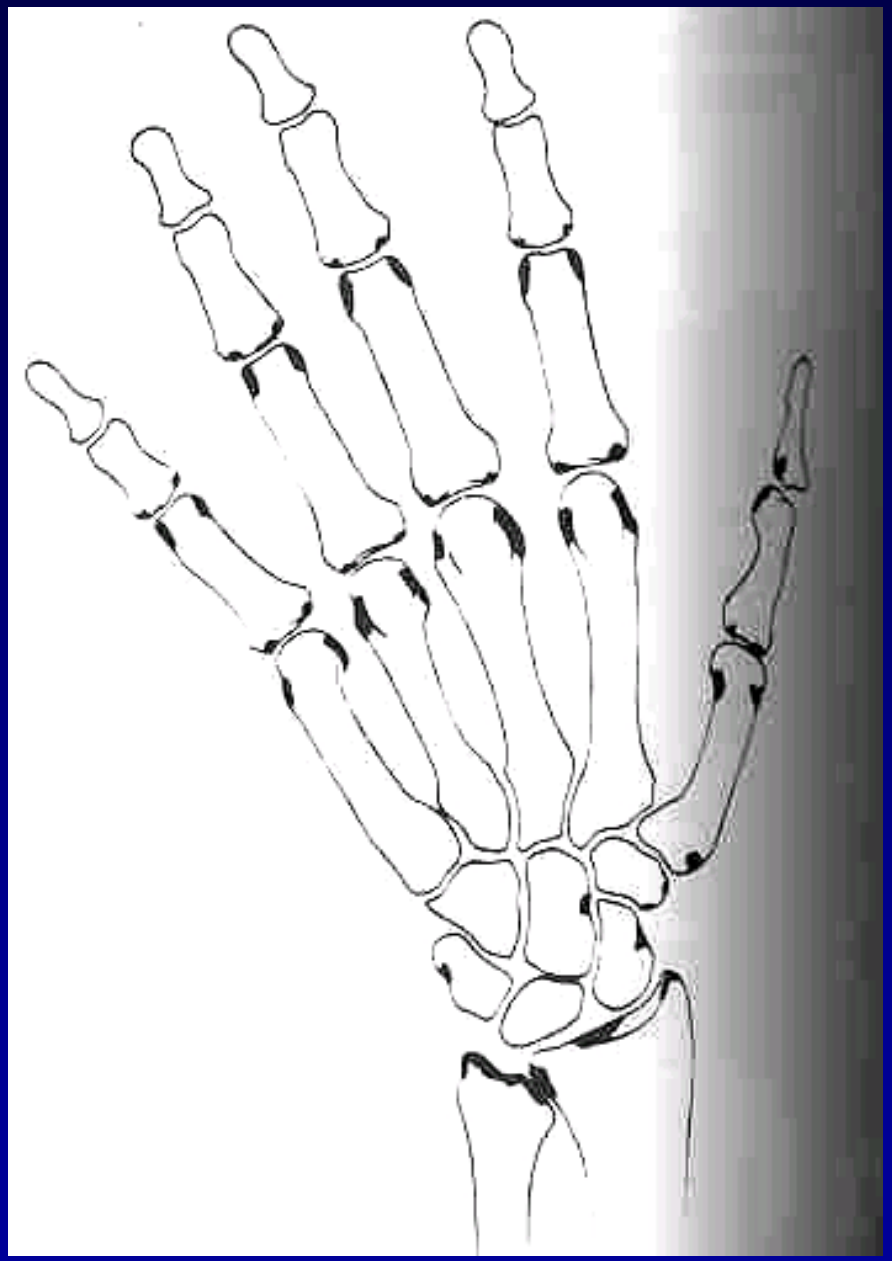
- “Cock up” or “claw” toe deformity
- Plantar subluxation of metatarsal head
- “walking on marbles”
- Pressure Necrosis
- Callouses



Rheumatoid Arthritis : rheumatoid nodules



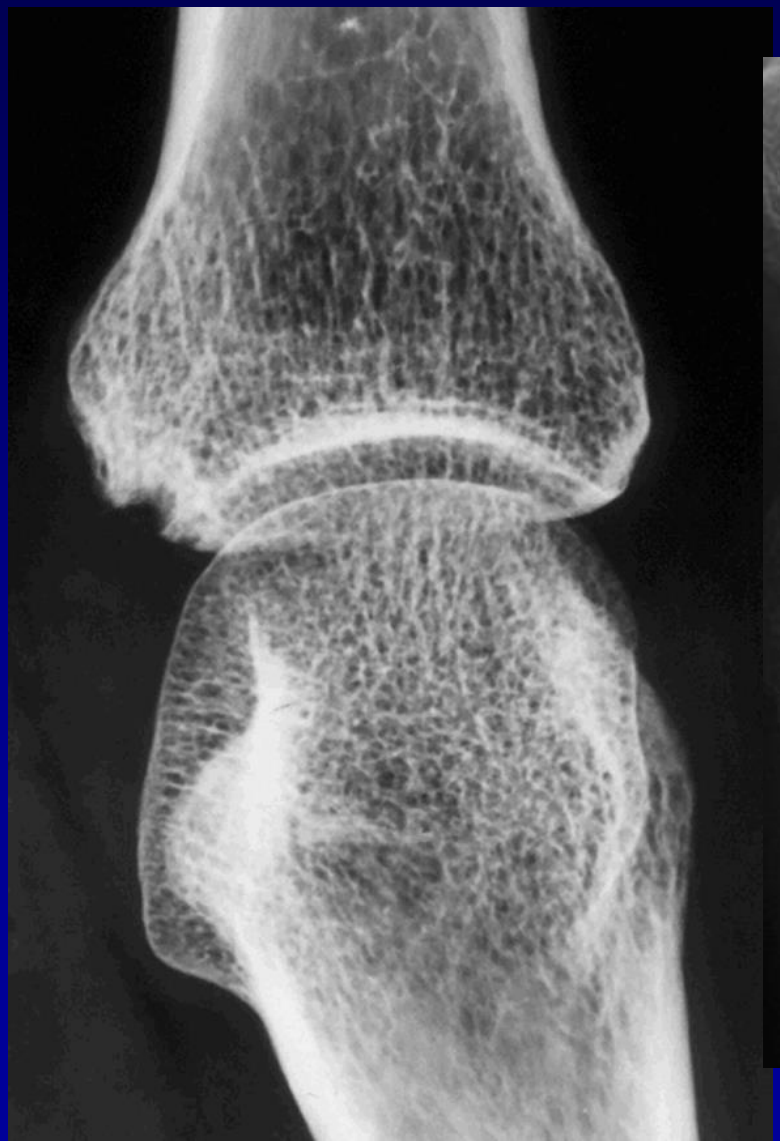
- SubQ, firm, usually mobile, less commonly adherent
- Central area of necrosis rimmed by a corona of palisading fibroblasts
  - surrounded by a collagenous capsule with perivascular inflammatory cells
- DDx: Rheumatic fever, granuloma annulare, gouty tophi, multicentric reticulohistiocytosis, SLE, xanthomatosis

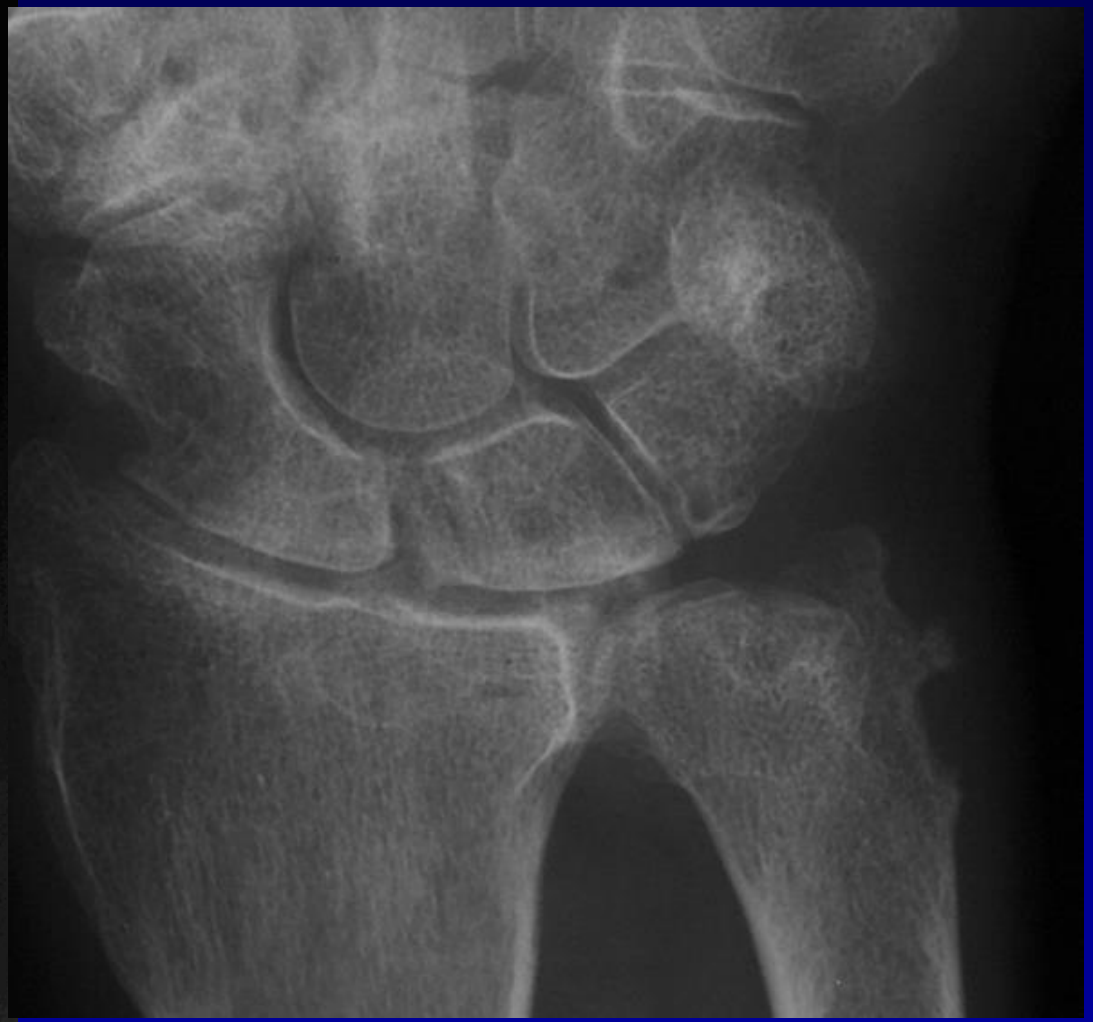


Marginal regions or “bare areas” in the hand susceptible to attack by rheumatoid pannus

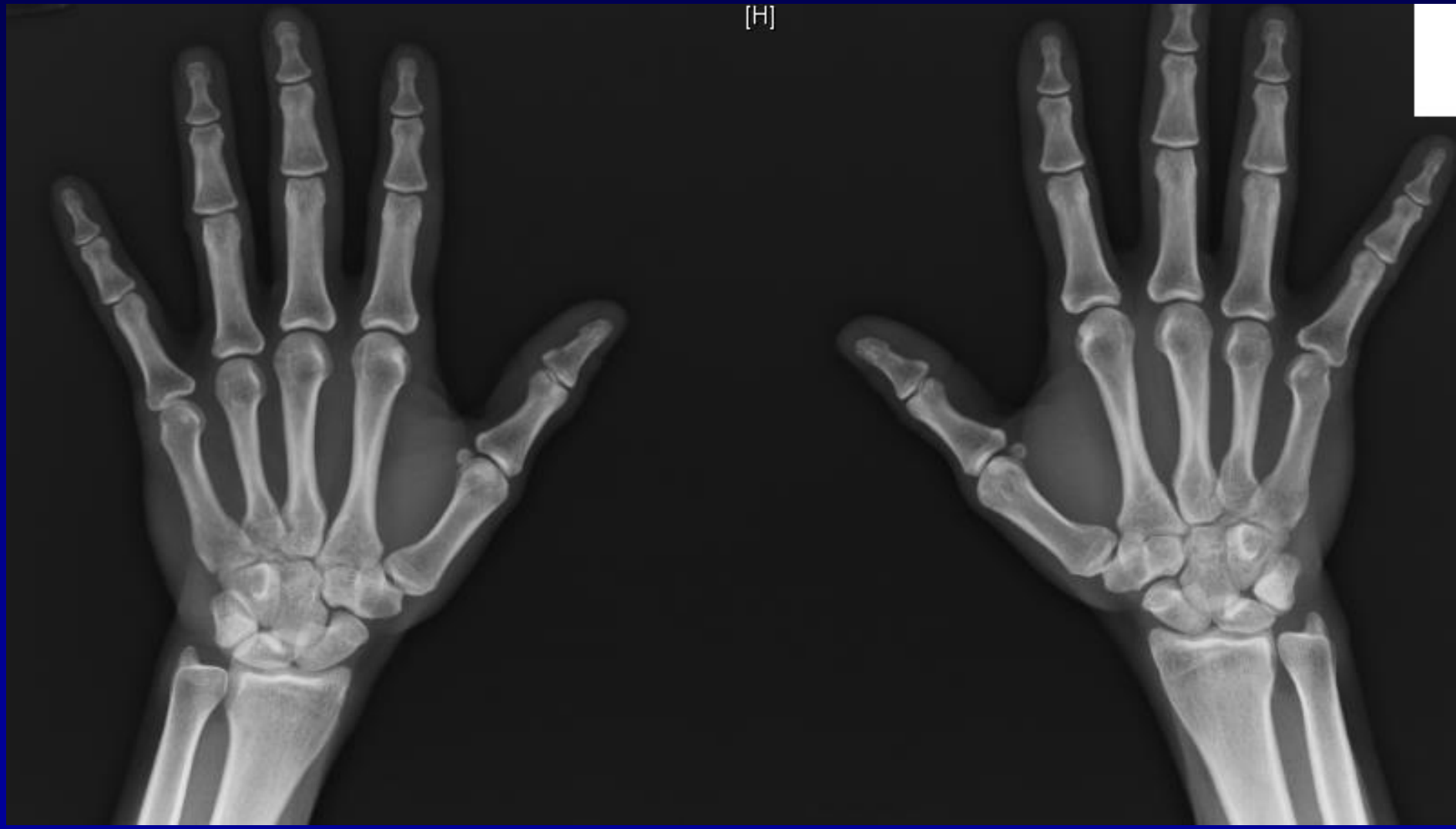
NOTE: not all “erosions are RA”

RA : erosions

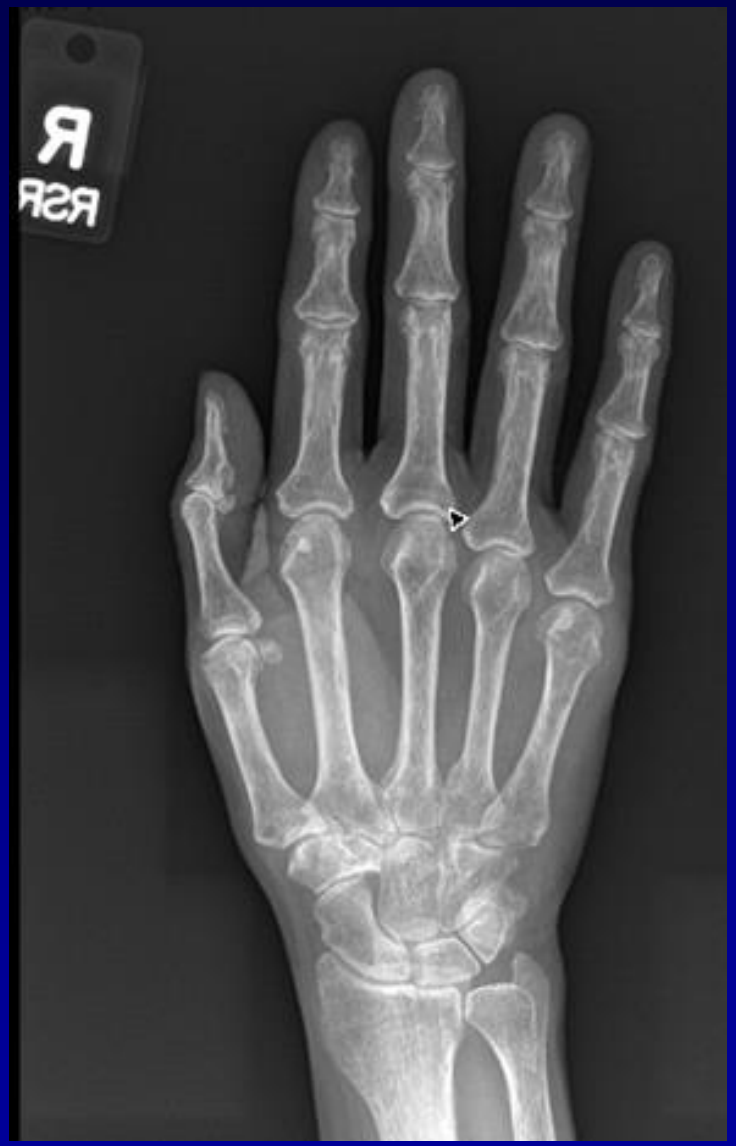




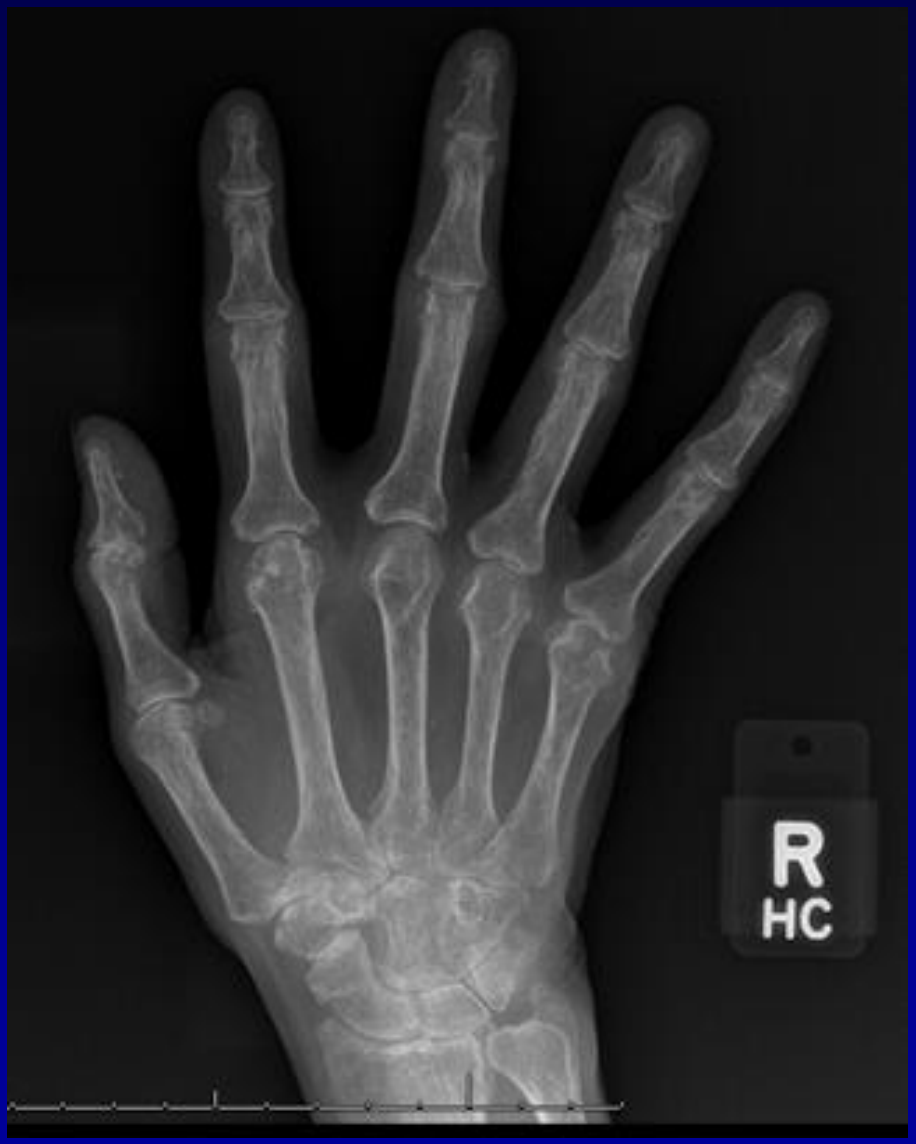
Early RA



RA : Progressive Xray Damage

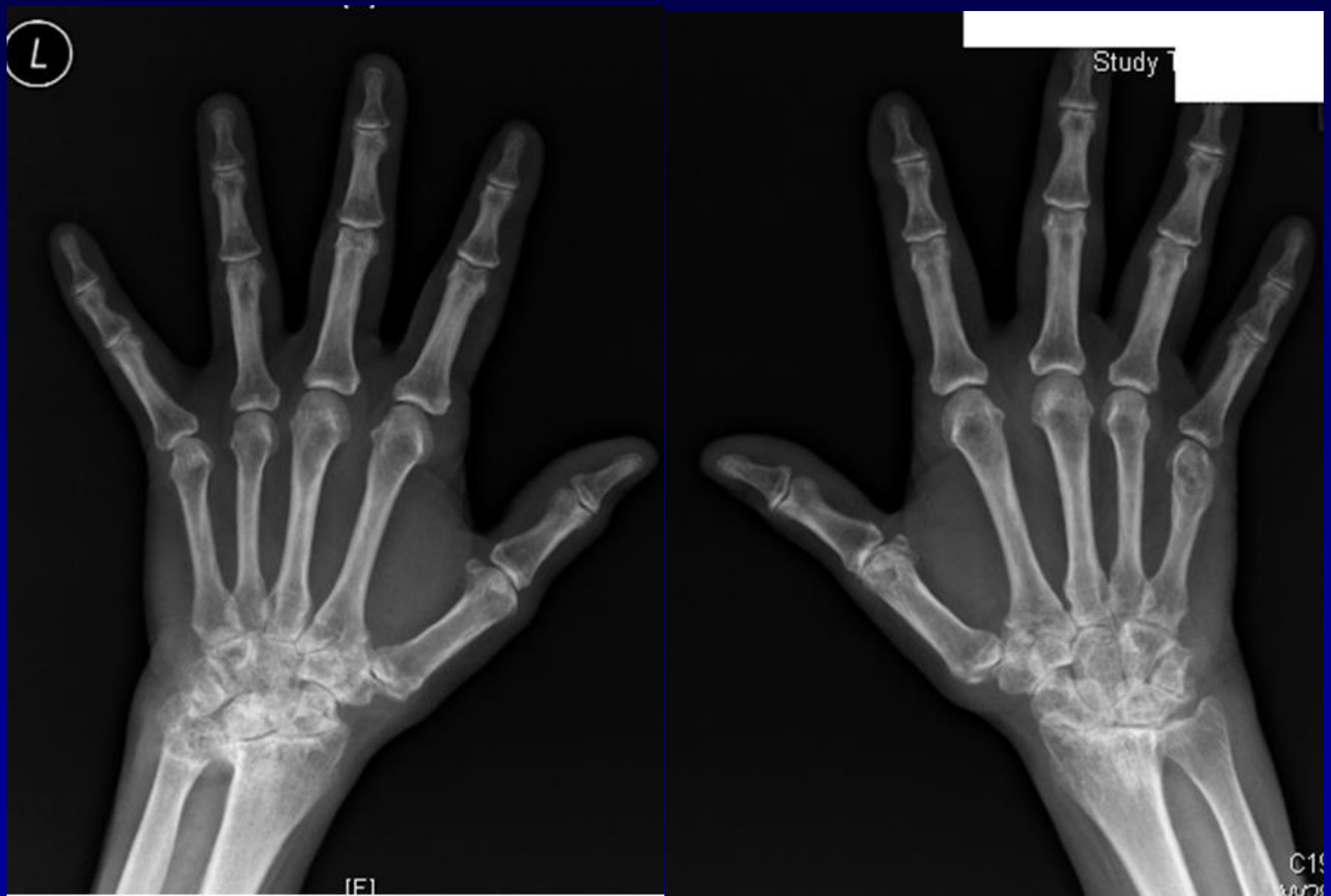


2009

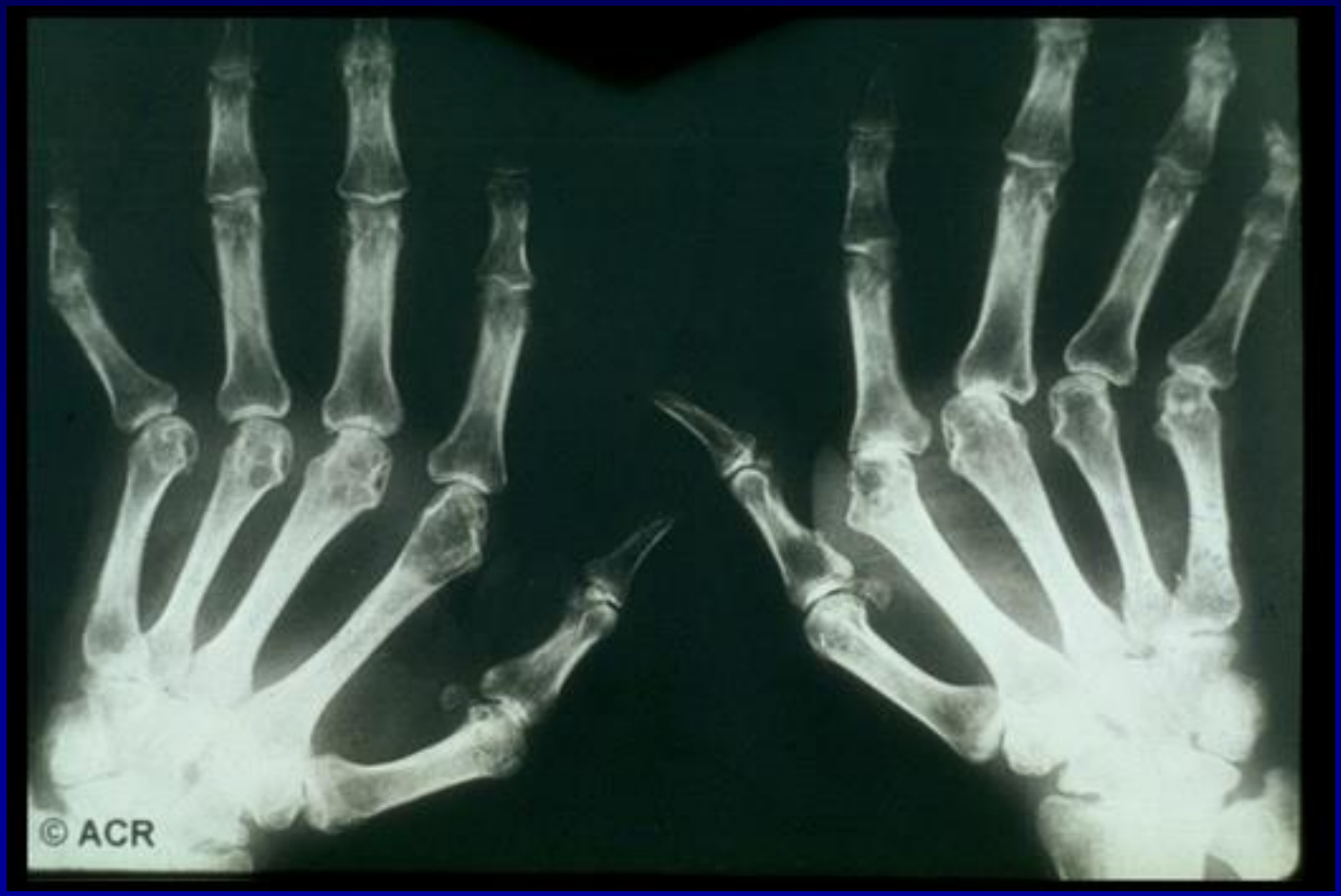


2014

Advanced RA



RA : Radiographic Changes

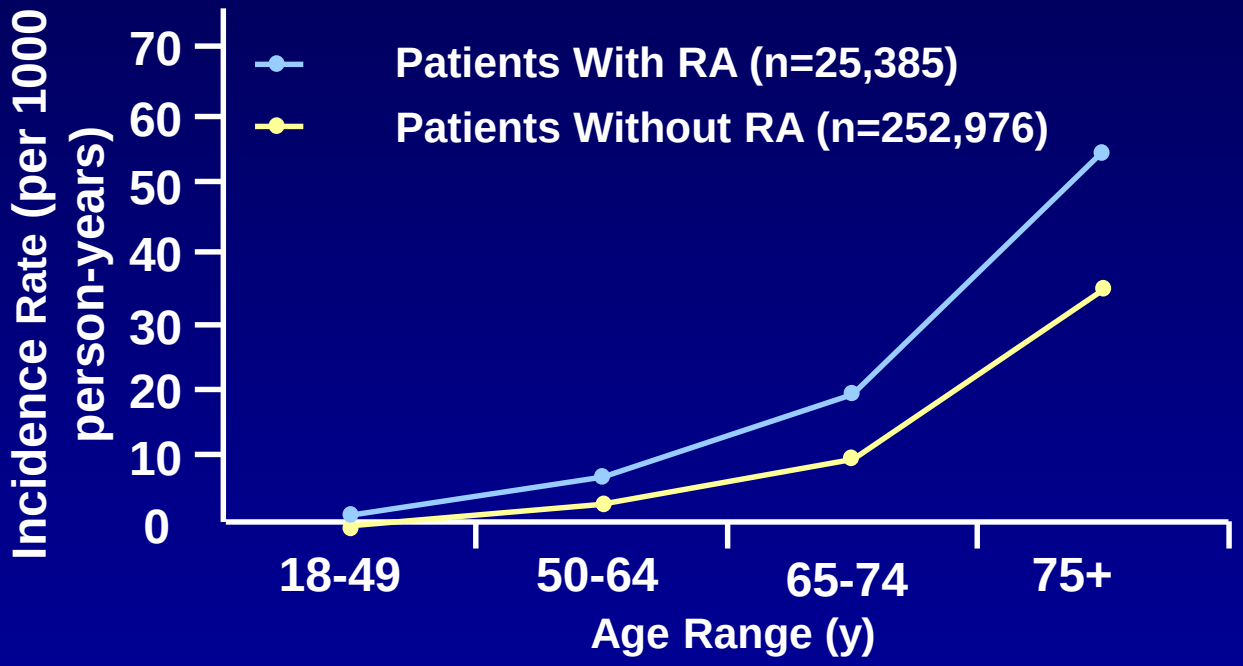


RA Complications and Comorbidities

Cardiovascular Disease	Cancer	Infections	Other Extra-Articular Diseases
• Myocardial infarction	• Lymphoma	• General	• Sjögren's syndrome
• Heart failure	• Lung cancer	• Bacterial	• Vasculitis
• Stroke	• Skin cancers		• Hematologic
• Peripheral vascular disease			• Interstitial lung disease
• Hypertension			• GI disease
			• Osteoporosis
			• Renal amyloid
			• Neuropathy
			• Epi/scleritis
			• Depression

Scott DL, et al. *Lancet*. 2010;376:1094-1108.

RA Is an Independent Risk Factor for Cardiovascular Events*

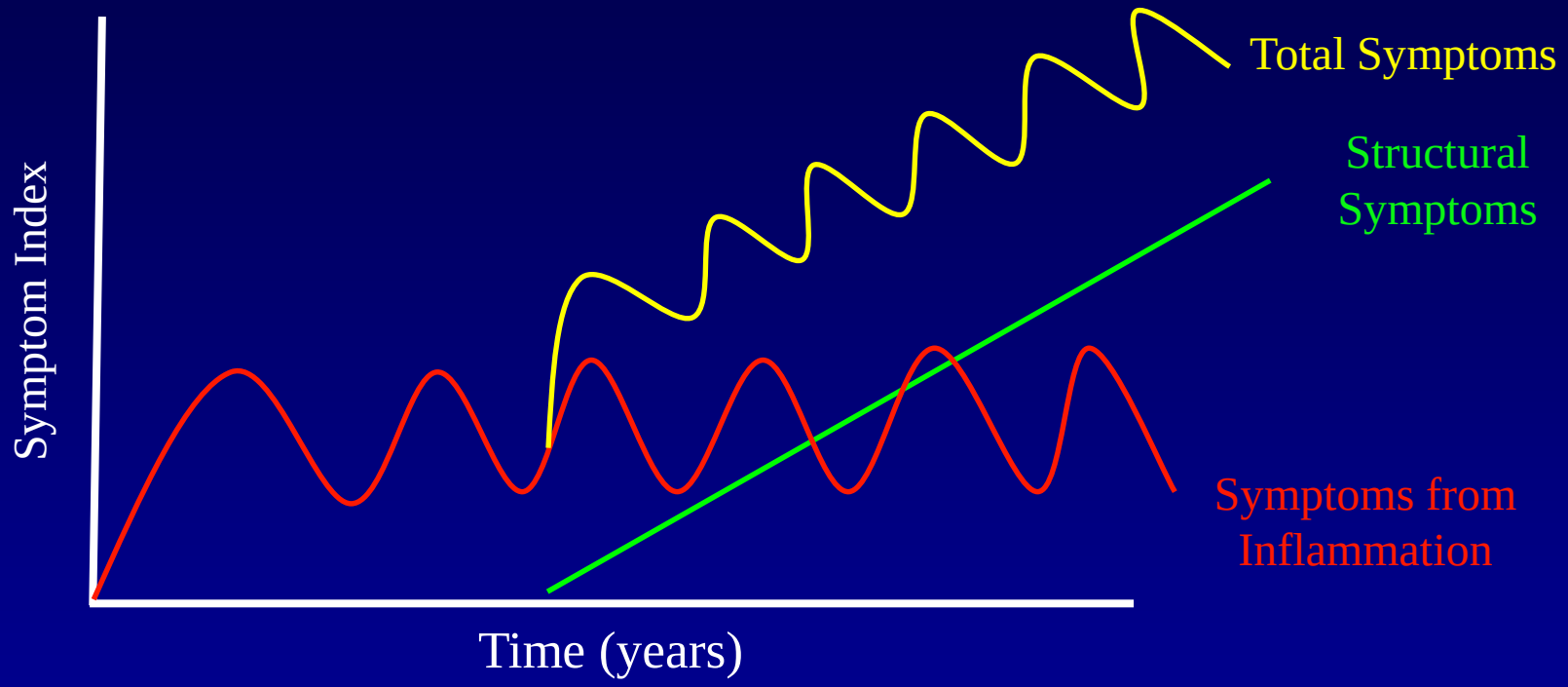


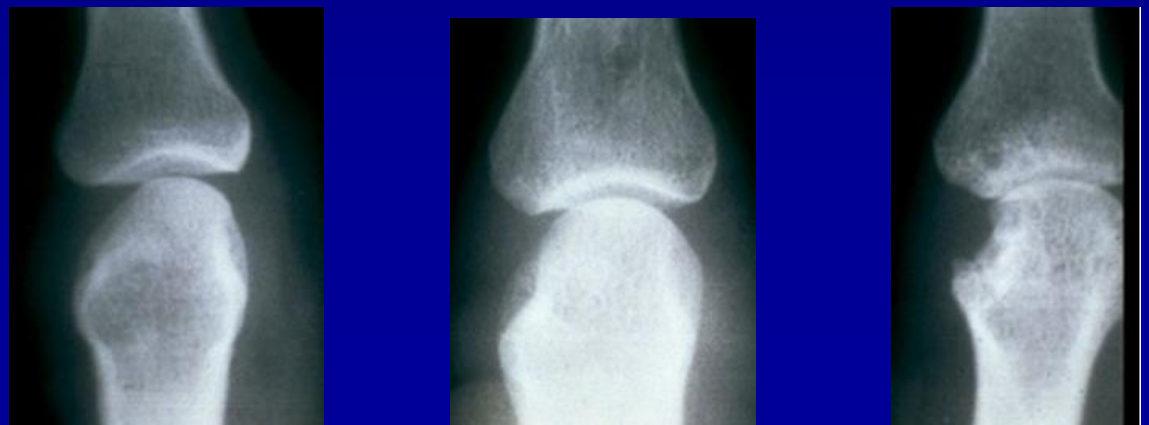
- RR 1.8 for MI
- RR 1.9 for stroke
- RR 1.3 for CV death
- RR 1.6 for any above
  - 18-49 yo : RR 3.3
  - >65 yo : RR 1.6-1.9

*Myocardial infarction, stroke

Solomon DH et al. *Ann Rheum Dis*. 2006;65:1608-1612.

Rheumatoid Arthritis : Clinical Course



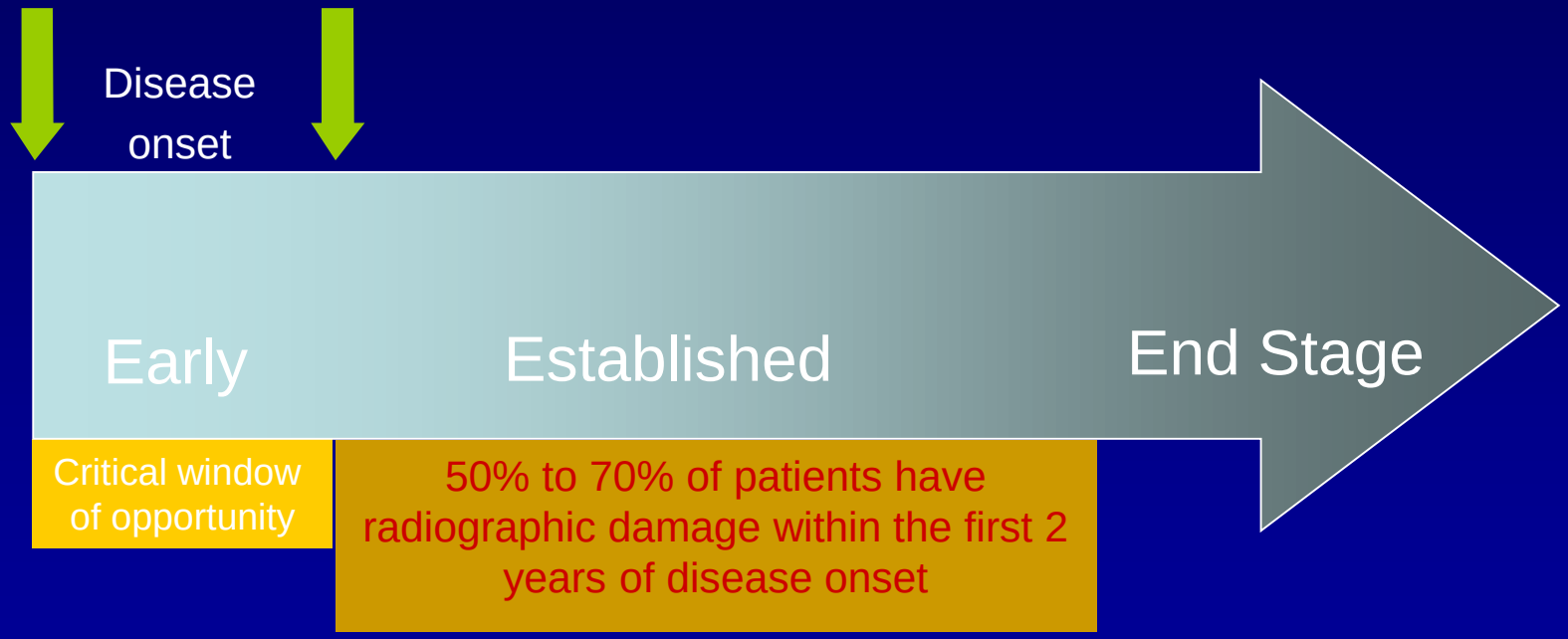


RA : TREATMENT

ACR Recommendations: Early Aggressive Treatment of Rheumatoid Arthritis

"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."

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



ACR Subcommittee on RA Guidelines. *Arthritis Rheum.* 2002;46(2):328-346.
Van der Heijde DM, et al. *Br J Rheumatol.* 1995:34(suppl 2):74-78.
Quinn MA, et al. *Rheum Dis Clin N Am.* 2005;31:575-589.

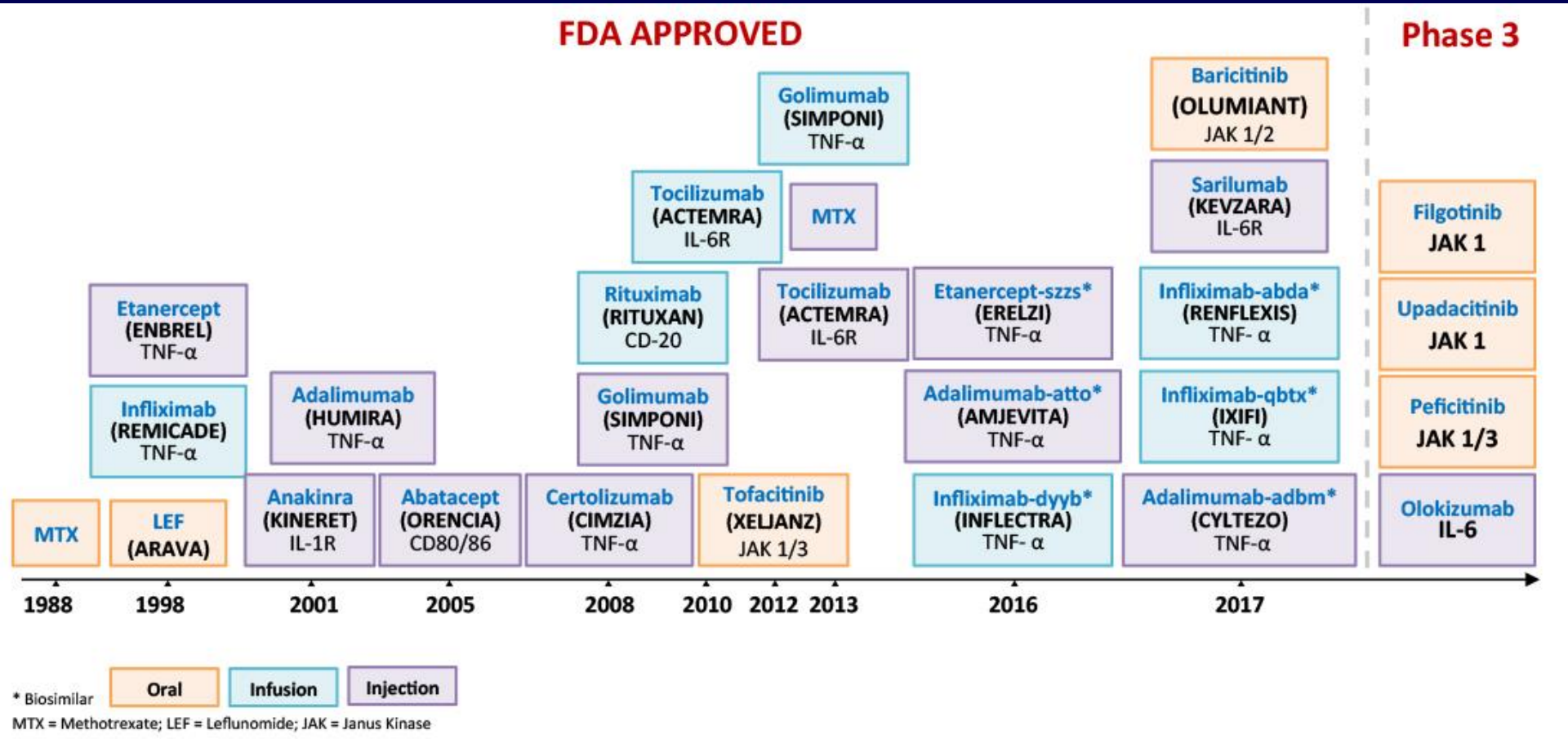
Core Principles in RA Management

- Early recognition and diagnosis
- Early use of DMARDs
- Treat-to-target (T2T)
- Target of remission or low disease activity
- Frequent monitoring of disease activity
- Individualized treatment

DMARDs = Disease-Modifying Antirheumatic Drugs.

Singh JA, et al. *Arthritis Rheumatol*. 2016;68(1):1–26; Singh JA, et al. *Arthritis Care Res*. 2016;68(1):1–25; Smolen JS, et al. *Ann Rheum Dis*. 2014;73(3):492–509; Smolen JS, et al. *Ann Rheum Dis*. 2010;69(4):631–637; Smolen JS, et al. *Ann Rheum Dis*. 2016;75(1):3–15.

Rheumatoid Arthritis : Treatment landscape



Rheumatoid Arthritis : Available Therapeutics

DMARDS

- Antimalarials, (hydroxycholorquine
- Sulfasalazine
- Methotrexate
- Leflunomide (Arava)

- Biologics
  - TNFα inhibitors
    - Subcutaneous → Etanercept (Enbrel) , Adalimumab (Humira), Golimumab (Simponi), Certolizumab pegol (Cimzia)
    - Intravenous →Infliximab (Remicaide), Golimumab (Simponi aria)
  - IL1 blockade
    - Anakinra, IL1 receptor antagonist (Kineret)
  - Tcell costimulation inhibitor
    - Abatacept (SQ, IV) (Orencia)
  - Bcell depeltion
    - Rituximab (Rituxan)
  - IL-6 receptor blockage
    - Tocilizumab (Actemra), Sarilumab (Kevzara)
- JAK Inhibitors : Tofacitinib (Xeljanz), baracitinib (Olumiant), upadacitinib (Rinvoq)
- NSAIDS
- Corticosteroids

RA: Methotrexate

- Aminopterin (folic acid antagonist) beneficial in 7 of 8 “rheumatoid arthritis” patients (Am J of Med Sci. 1951)
- Uncontrolled trials of low dose intermittent methotrexate in RA
  (RF Wilkens et al. J Rheum. 1980)
  (K Steinsson et al. J Rheum. 1982)
- RCT of low dose methotrexate in RA (ME Weinblatt et al. NEJM. 1985)
  - 35 patients, double blind cross over study, placebo controlled, 24 weeks
  - 12 weeks : MTX group with fewer swollen and tender joints, improved grip strength, less morning stiffness
  - 24/33 patients who received mtx (73%) had at least a 30% improvement in the joint-tenderness/pain index
  - 20/33 patients who received mtx (61%) had at least a 30% improvement in the joint-swelling index

Methotrexate in RA

- Should not be used in patients with hepatic or renal dysfunction
- Patients should abstain from alcohol and use appropriate birth control
- Laboratories to obtain prior to starting:
  - BUN/Cr
  - Liver function tests
  - CBC
  - Hepatitis C and B panel
- Given one day per week,
  - start with 7.5 mg one day per week
  - average dose ~17.5 mg one day per week
  - folic acid 1-2 mg daily
- Laboratories to obtain for monitoring of toxicity
  - Bun/Cr, ALT, AST, Albumin, CBC every 6-8 weeks

Methotrexate : RA and Mortality

- Subjects : RA patients seen at the Wichita Arthritis Center between 1981 and 1999 who had not been previously treated with methotrexate
- Cohort study comparing all cause mortality (primary outcome) in patients who received methotrexate (n=588) vs those who have not (n=660)
- MTX group had more severe RA
- 191/1240 RA patients died
  - 72 in mtx group, 119 in control group

	ICD-9 code	Deaths	Hazard ratio (95% CI)*
All-cause mortality	All	191	0·4 (0·2–0·8)
Cardiovascular mortality	390–449	84	0·3 (0·2–0·7)
Non-cardiovascular mortality	<390 or >449	107	0·6 (0·2–1·2)

*Estimated from weighted Cox models adjusted for age, sex, rheumatoid factor, calendar year, duration of disease, smoking, education, health assessment questionnaire score, patient global assessment, joint counts, erythrocyte sedimentation rate, prednisone status, and number of other disease-modifying antirheumatic drugs used.

Table 2: **Mortality hazard ratio for methotrexate use compared with no methotrexate use**

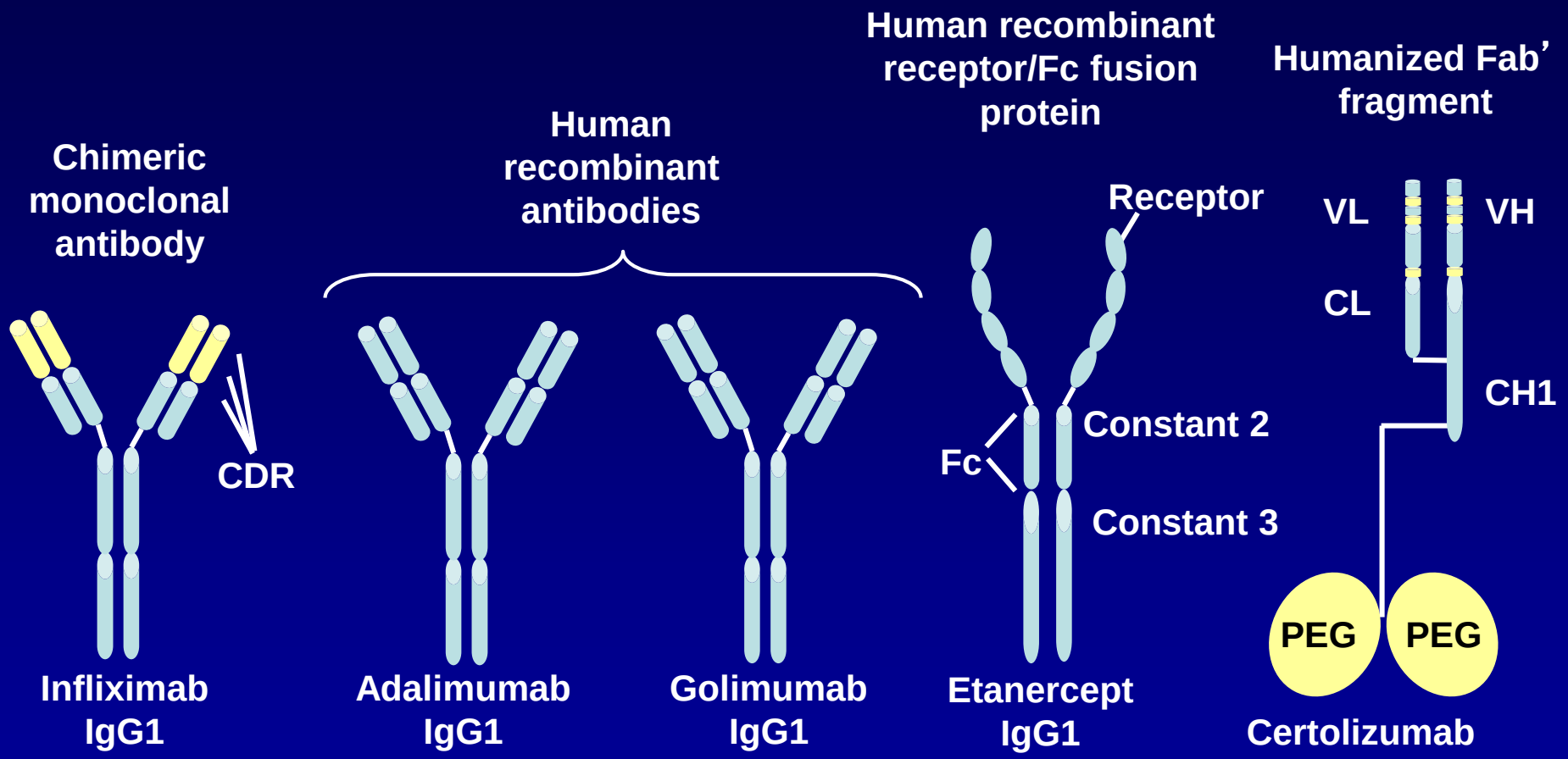
HK Choi et al. Lancet. 2002

Traditional DMARDs for RA

Agent	Usual Dosage	Adverse Effects	Monitoring
Methotrexate	10–25 mg weekly (oral or subcutaneous)	Hepatotoxicity, myelotoxicity, pneumonitis	CBC and CMP every 8 weeks
Sulfasalazine	1,000–1,500 mg twice daily (oral)	Hepatotoxicity, myelotoxicity	CBC and CMP every 3-4 months
Leflunomide	10–20 mg daily (oral)	Hepatotoxicity, myelotoxicity	CBC and CMP every 8 weeks
Hydroxychloroquine	400–600 mg daily Maintenance dosing 200 mg to 400 mg daily (oral)	CNS, neuromuscular, ocular, dermatologic, and GI reactions	Annual ophthalmology exam
Glucocorticoids	Varies	Osteoporosis, elevation of blood sugar, infection, weight gain, etc etc	Bone density if prolonged steroids

Sweiss N, Hushaw LL. *J Infus Nurs.* 2008;32(15):S4-S17.
van Vollenhoven RF. *Nat Rev Rheumatol.* 2009;5:531–541.

Molecular Structures of TNF-α Inhibitors*



Mouse
Human

CDR=Complementarity–determining region
PEG=Polyethylene glycol

*Structural differences not indicative of differences in efficacy or safety.

Adapted from Tracey D et al. *Pharmacol Ther*. 2008;117:244-279

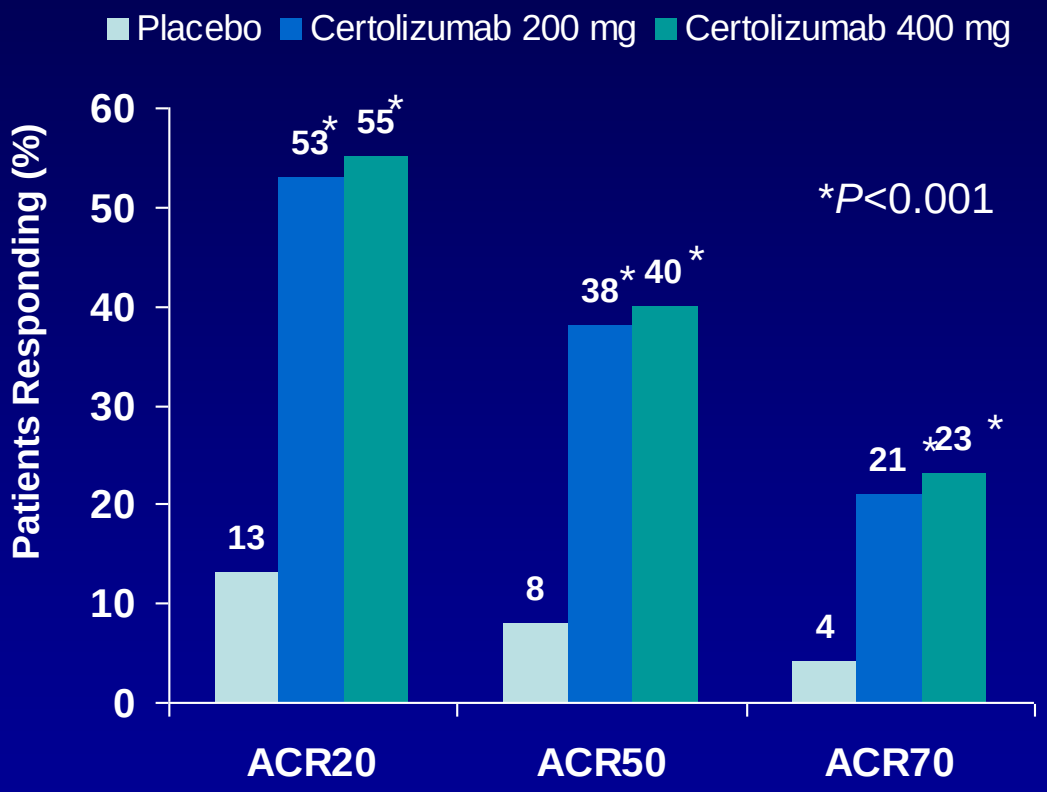
RA Treatment : TNF inhibitors

Study	Treatment	ACR20 (%)	ACR50 (%)	ACR70 (%)
Moreland et al. NEJM 1997	Placebo	11	5	1
	Etanercept	**59**	40	15
Weinblatt et al. NEJM 1999	Methotrexate	27	3	0
	Etanercept + methotrexate	**70**	39	15
Maini et al. Lancet 1999	Methotrexate	20	5	0
	Infliximab + methotrexate	**50**	27	8
Weinblatt et al. Arth Rheum 2003	Methotrexate	15	8	5
	Adalimumab + methotrexate	**67**	55	27

TNFα Inhibition: Certolizumab Pegol

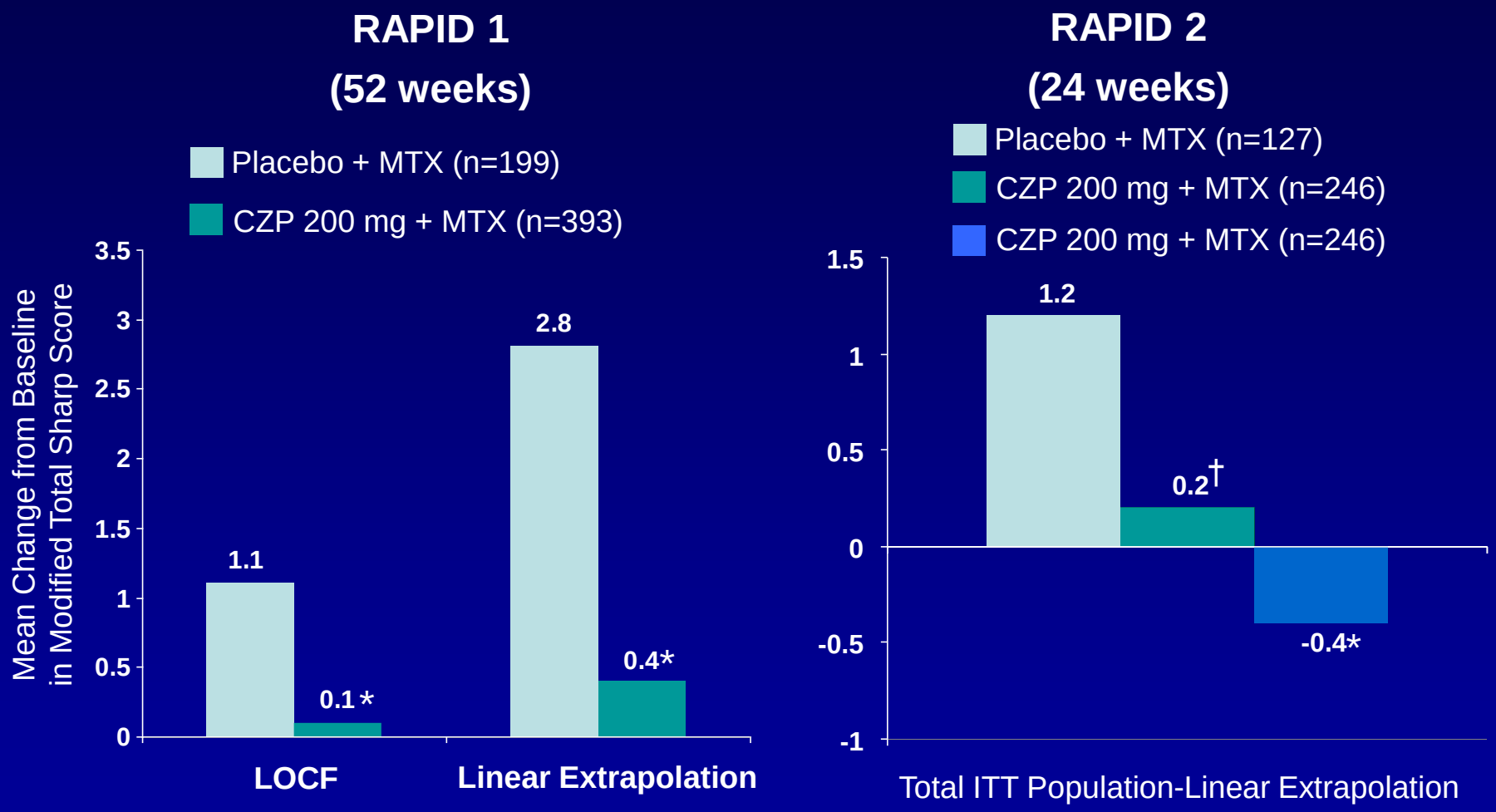
RAPID 1

- Phase 3, 52-week RCT, N=982
- Background MTX
- Loading dose to improve early response
- Patients randomized to:
  - Certolizumab 400 mg doses every 2 weeks, followed by doses of 200 mg
  - Certolizumab 400 mg every 2 weeks
  - Placebo



Keystone EC et al. *Ann Rheum Dis.* 2008;67:186.

RAPID 1 and 2: Certolizumab Pegol Effects on Radiographic Outcomes in RA



*P<0.001; †P≤0.01 vs placebo.

Keystone E et al. *Arthritis Rheum*. 2008;58:3319-3329. Smolen JS et al. *Arthritis Rheum*. 2008.

RA : Combination Therapy

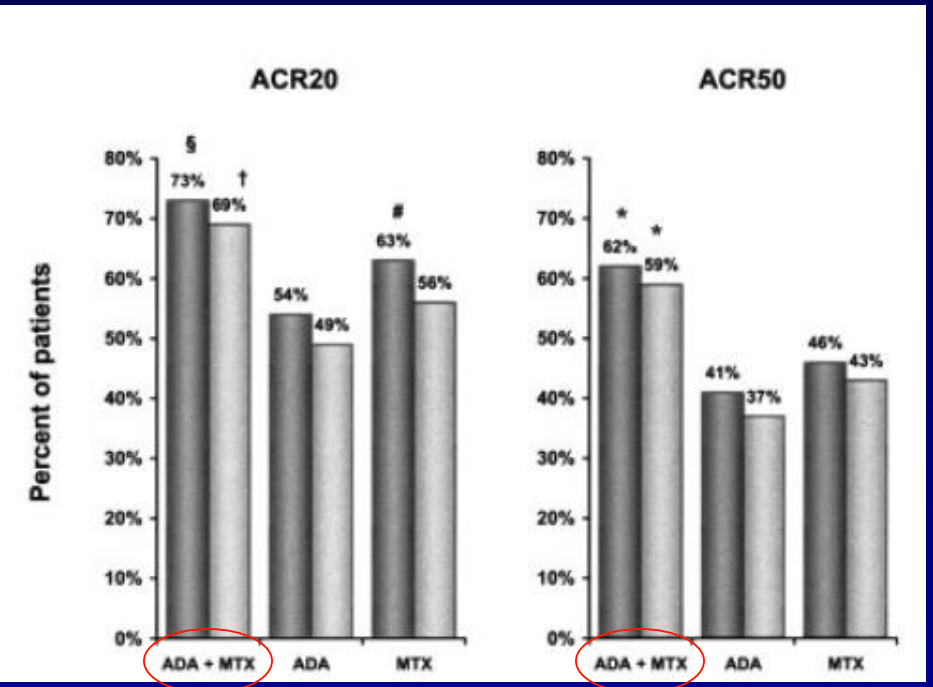


Table 2. Low disease activity and remission at 6, 12, and 24 months*

	LOCF		
	MTX (n = 228)	Etan. (n = 223)	Etan. + MTX (n = 231)†
Low disease activity			
DAS <2.4			
Week 24	31.6	31.8	51.1
Week 52	35.1	38.6	61.0
Week 100	38.6	44.4	65.4
DAS28 <3.2			
Week 24	22.8	26.5	45.0
Week 52	29.4	32.3	53.2
Week 100	28.5	33.2	58.4
Remission			
DAS <1.6			
Week 24	13.6	13.0	29.9
Week 52	14.0	17.5	37.2
Week 100	15.8	23.3§	40.7
DAS28 <2.6			
Week 24	13.6	13.9	30.3
Week 52	17.1	17.5	38.1
Week 100	18.9	22.4	42.4

PREMIER Trial

MTX vs Adalimumab vs Both

TEMPO Trial

MTX vs etanercept vs both

FC Breedveld et al . Arth Rheum 2006

D ven der Heijde et al. Arth Rheum. 2006

TNF inhibitors : adverse events

- Infections
  - TB and Reactivation of TB
    - Screen by taking a history for TB exposures
    - Annual skin test or Quantiferon gold +/- CXR
    - Treat with INH/B6 for 6-9 months
  - Opportunistic infections
  - Listeria, histoplasmosis, coccidiomycosis
  - Cellulitis, viral syndromes
  - Hepatitis
    - Increased viral burden in HepB
    - OK in HepC
- Injection site reactions
- Infusion reactions
- Malignancy
- Leukopenia, pancytopenia, aplastic anemia
- Worsening of NHYA Class III/IV heart failure
- +ANA, +dsDNA, SLE like illness
- Demyelinating illness
- Psoriatic skin lesions

Biologic Trials in RA

- For the interest of time-

- Clinical trials support the effectiveness of all FDA approved biologics with regards to treatment synovitis and symptoms of RA as well as preventing radiographic progression of RA

  - TNFα inhibitors
    - Subcutaneous → Etanercept (Enbrel) , Adalimumab (Humira), Golimumab (Simponi), Certolizumab pegol (Cimzia)
    - Intravenous →Infliximab (Remicaide), Golimumab (Simponi aria)
  - Tcell costimulation inhibitor
    - Abatacept (SQ, IV) (Orencia)
  - Bcell depeltion
    - Rituximab (Rituxan)
  - IL-6 receptor blockage
    - Tocilizumab (Actemra), Sarilumab (Kevzara)

RA Biologics, special considerations

- All increase the risk of infections
- All should be screened for TB prior starting and annually thereafter

- TNF inhibitors (Etanercept, Infliximab, Adalimumab, Golimumab, Certolizumab pegol)
  - Malignancy
  - Congestive heart failure
  - Hepatitis B
  - Demyelination

- Abatacept
  - Chronic obstructive pulmonary disease (COPD)

- Tocilizumab, sarilumab
  - Liver toxicity
  - LDL elevation
  - Neutropenia, thrombocytopenia
  - Gastrointestinal perforations

- Rituximab
  - PML
  - Hepatitis B

Cytokine Receptors and JAKs

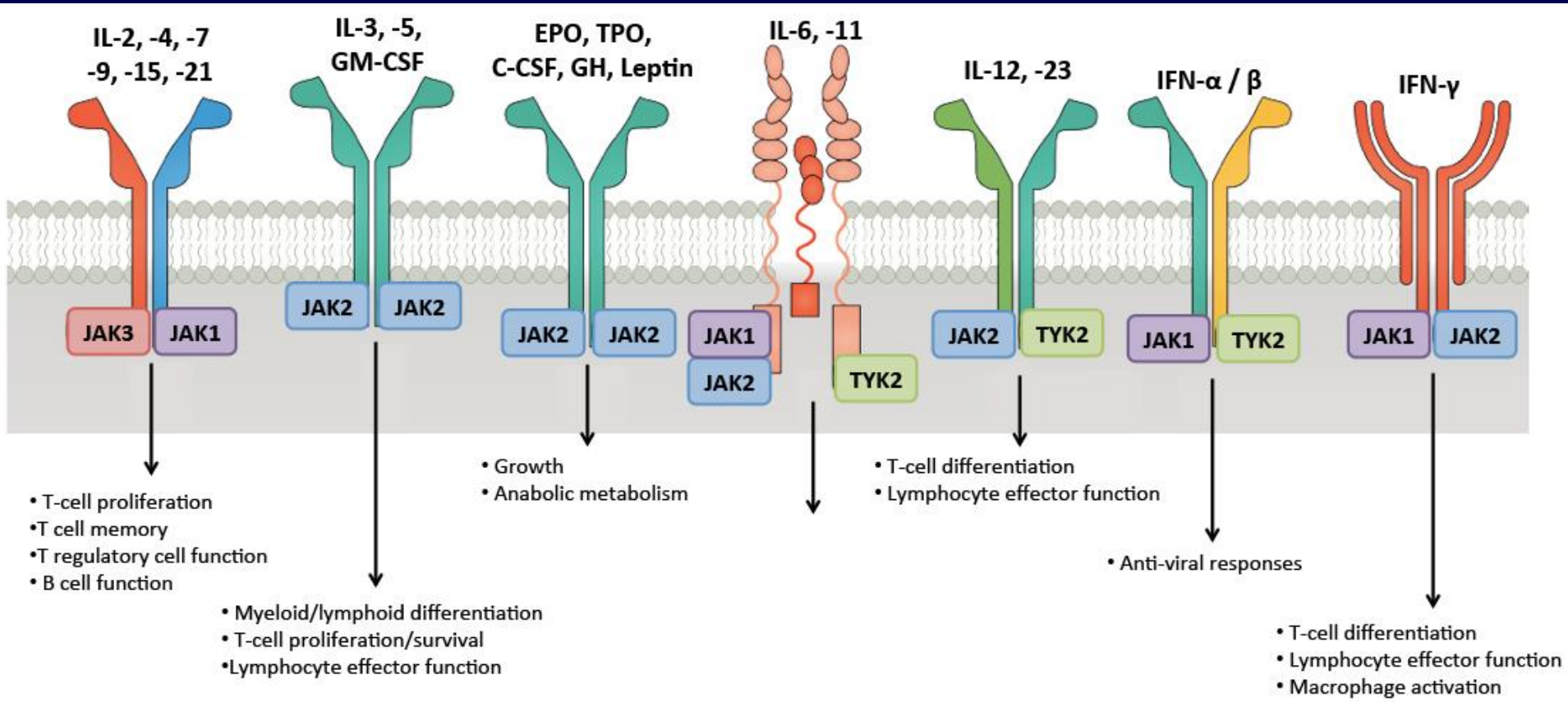
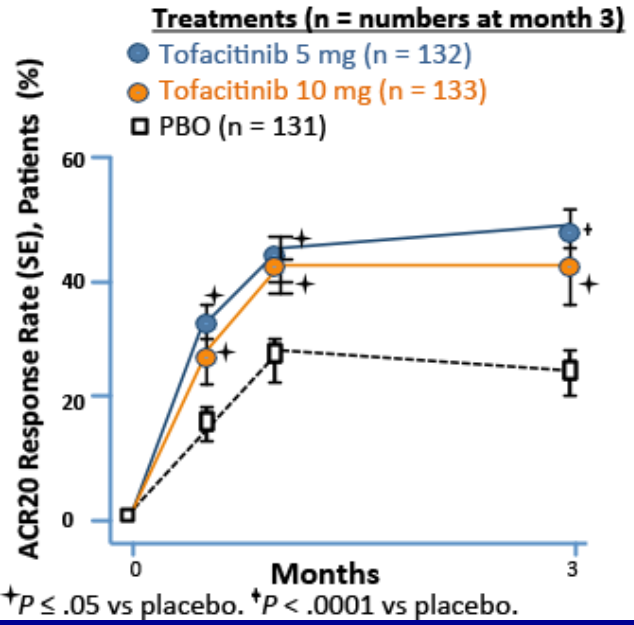


Figure adapted from Schwartz DM, et al. *Nat Rev Drug Discov*. 2017;16(12):843–862; Nakayamada S, et al. *BioDrugs*. 2016;30(5):407–419.

Efficacy and Safety of Tofacitinib (JAK 1/3) + MTX in TNFi-IR Patients

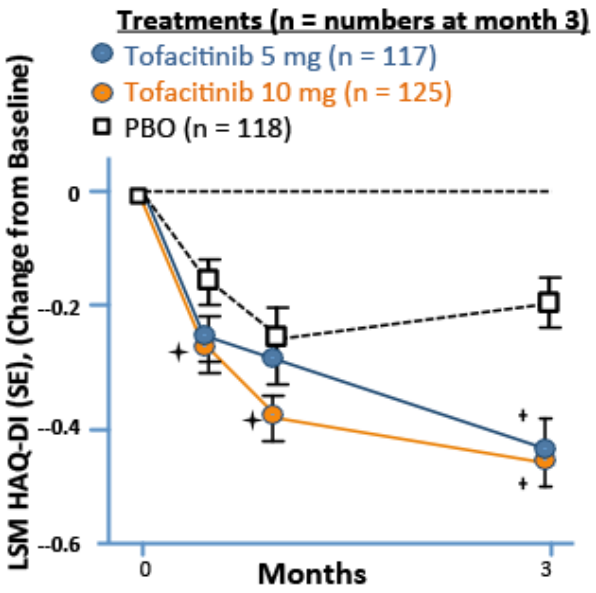
Phase 3 Trial Outcomes

ACR20 Response Rate (3 mos)

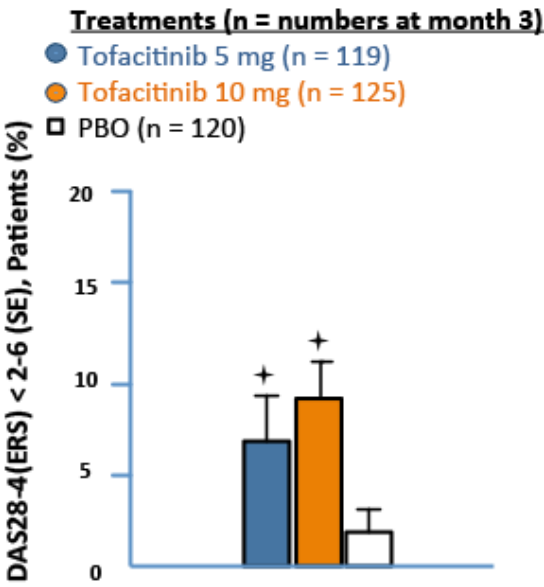


$^{+}P \leq .05$ vs placebo. $^{\ddagger}P < .0001$ vs placebo.

Change in HAQ-DI (3 mos)

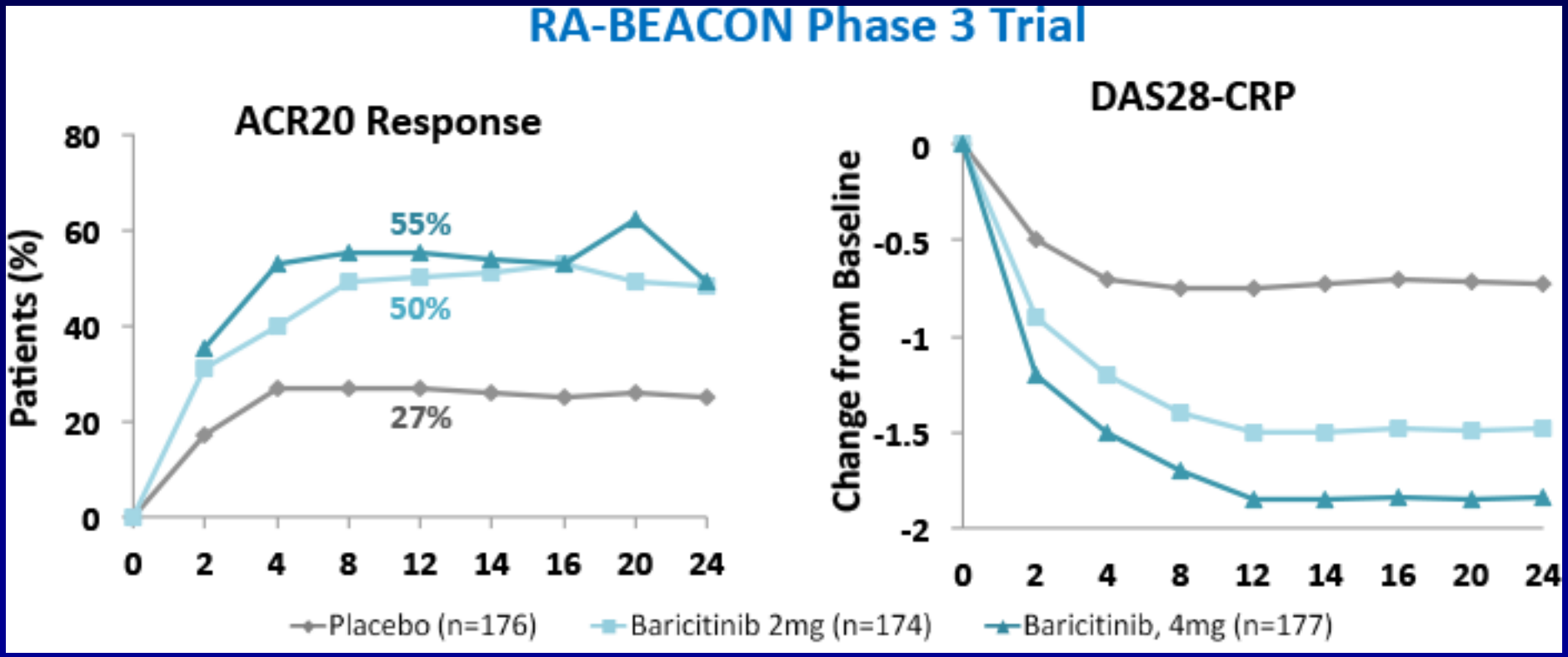


DAS28 < 2.6 (3 mos)



Burmester GR, et al. *Lancet*. 2013;381(9865):451-460; Wollenhaupt J, et al. ACR/ARHP 2017. San Diego, CA. Abstract 522; Kremer J, et al. EULAR 2019. Madrid, Spain. Abstract OP0028.

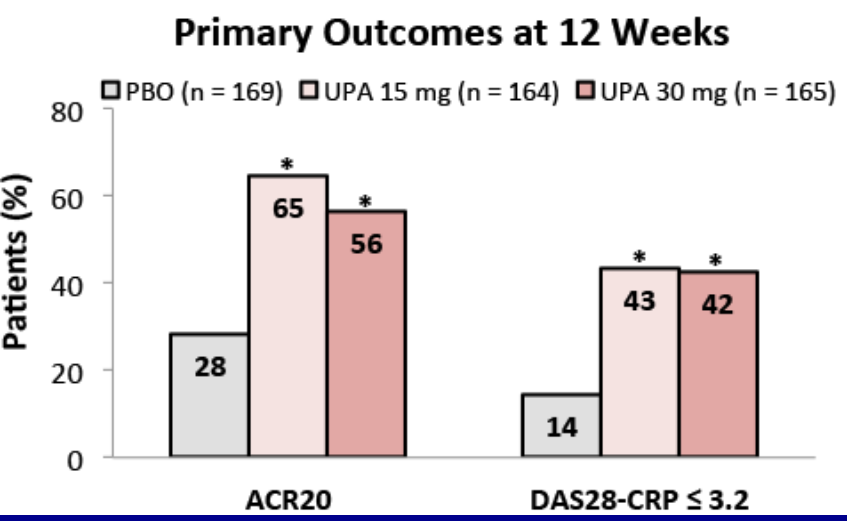
Efficacy and Safety of Baricitinib (JAK 1/2) in bDMARD-IR Patients

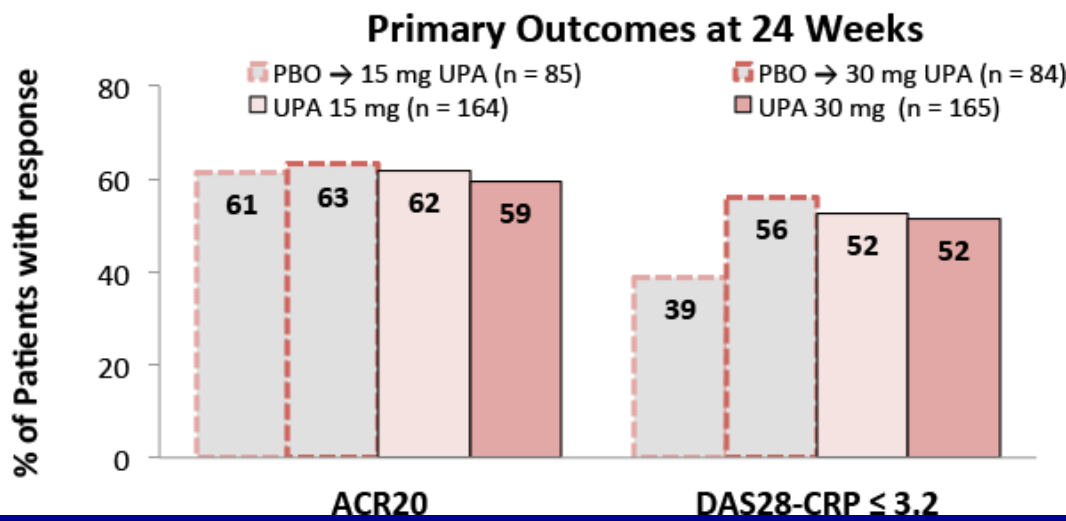


Genovese MC, et al. *N Engl J Med*. 2016;374(13):1243-1252; Fautrel B, et al. ACR/ARHP 2017. San Diego, CA. Abstract 508; Genovese MC, et al. *Rheumatology (Oxford)*. 2018;57(5):900-908; Genovese MC, et al. EULAR 2019. Madrid, Spain. Abstract THU0078.

Efficacy and Safety of Upadacitinib (JAK 1) in bDMARD-IR Patients

Phase 3 Trial SELECT-BEYOND





*P < .001 relative to PBO.

UPA = Upadacitinib; QD = once daily; bDMARD= biologic DMARD; VTE = Venous Thromboembolic Events; MACE = Major Adverse Cardiovascular Events; PRO = Patient-Reported Outcomes

Genovese MC, et al. Lancet. 2018 Jun 23;391(10139):2513-2524; Kremer J, et al. EULAR 2019. Madrid, Spain. Abstract FRI0155; Cohen SB, et al. EULAR 2019. Madrid, Spain. Abstract THU0167; Genovese MC, et al. EULAR 2019. Madrid, Spain. Abstract THU0172.

JAK Inhibitors : Adverse events

- Increase risk of infections
- Herpes zoster/Shingles reactivation
- Elevations in LDL
- Reductions in neutrophil counts
- Elevated LFTs
- Increased risk of thrombosis (venous, arterial)
- Malignancy?

Fleischmann et al. NEJM. 2012; 367:495-507

Screening Prior to Biologics and JAK inhibitors

- Assess infection risk
- PPD or quantiferon gold for TB exposure
- Hepatitis B and C serologies
- CBC for cytopenias, lipid panel and CMP for baseline
- Screen for comorbities
  - Class III or IV CHF – avoid TNFi
  - COPD - avoid abatacept
  - Liver disease – avoid antiIL6r and JAKinhibitors

Vaccinations in adults with rheumatoid arthritis

- No lives vaccines in patients on biologics

- All patients who are treated should get pneumococcal vaccine, annual inactivated influenza vaccine (IM) and HBV vaccines
  - Influenza – use inactivated IM form, not nasal spray
  - Ideally family members should get influenza vaccine (not nasal spray)
  - Pneumococcus vaccine - PCV13 followed 8 weeks later by PPSV23
  - Preferably prior to immune suppression but would not delay immune suppression

- Herpes zoster should be done in patients over 50
  - Prefer recombinant (non-live) glycoprotein E vaccine (recombinant zoster vaccine, RZV, Shingrix)

Conclusions

- Rheumatoid arthritis is a common autoimmune form of arthritis
- RA patients can have premature coronary artery disease, osteoporosis and lung disease
- Early treatment with disease modifying anti-rheumatic drugs and/or biologics is effective is treating symptoms of RA and preventing damage to joints
- Treatment options continue to grow!
- Patients require monitoring for disease activity and adverse effects