ACP NH Annual Scientific Meeting-2019

Update on Biologics and Targeted Therapeutics in Rheumatologic Disease
October 25, 2019

William F.C. Rigby, M.D.
Vice-Chair, Academic Affairs
Department of Medicine
Professor of Medicine, Microbiology & Immunology
Staff Rheumatologist
Dartmouth-Hitchcock Medical Center
Lebanon, NH

Learning Objectives

- **What have we learned about biologics and targeted therapies?**
- **What about these meds will make your patient's day?**
- **What about these meds will ruin your patient's day (and yours)? What do I need to be vigilant about?**

Disclosures/Off Label Use

Consultant:

AbbVie, Amgen, BMS, Pfizer, Roche,

Clinical Trials & Research Grants:

AbbVie, Amgen, Gilead, Pfizer, Sun Pharma

No off label use will be discussed except to mention presence of clinical trials addressing these

The speaker is responsible for the content

Disclaimers

- Rheumatoid Arthritis (RA-Centric)
- Emphasis on the therapeutics of tomorrow
- Non-RA biologics NOT covered
  - Antibody mediated antagonism of IL-17, IL12/23, BAFF, used in PsA, AS, SLE
  - Indirect consideration of agents for other diseases (e.g. anti-IL6 in GCA, RTX in AAV)

Outline:

- RA Overview
- **RA Therapy**
- JAK Inhibitors
- Safety

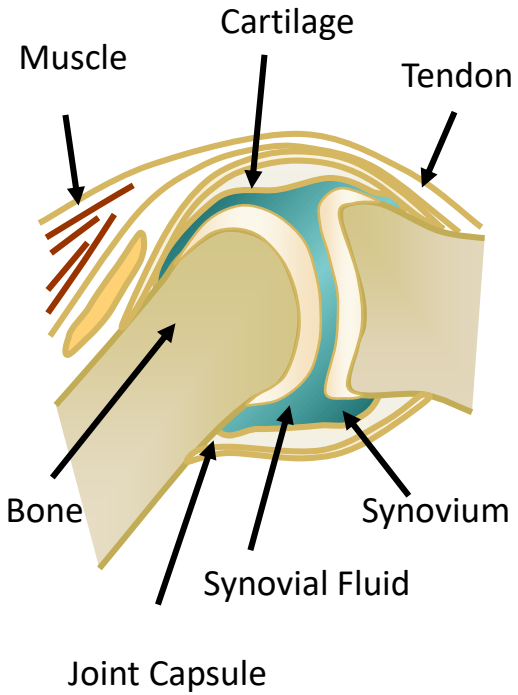
Rheumatoid Arthritis

Articular Disease:

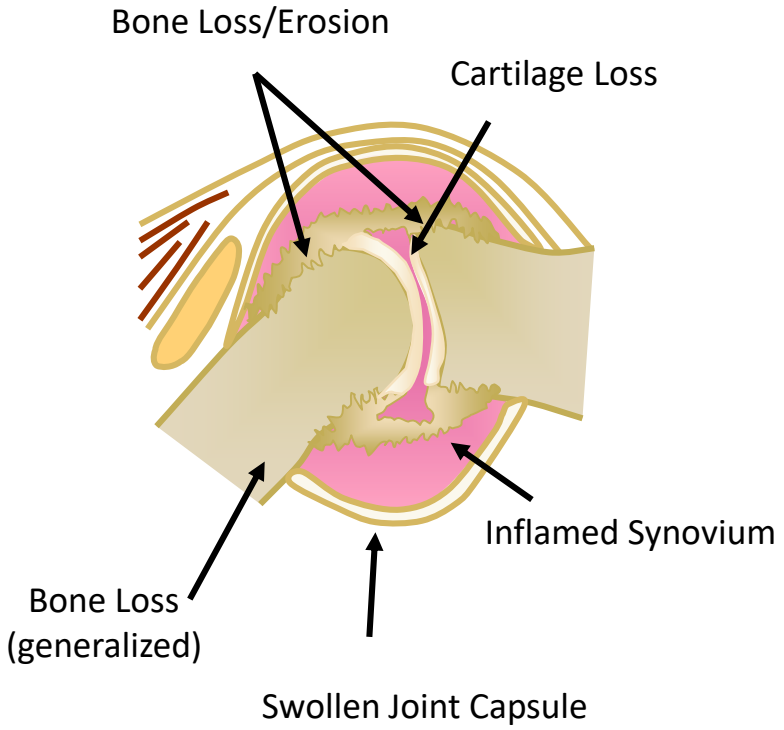
- Presentation (women>men 4:1)
- Synovial inflammation
- Seropositive and Seronegative
- Strong HLA-DR linkage

Difference Between Normal Joint and Joint Affected by RA

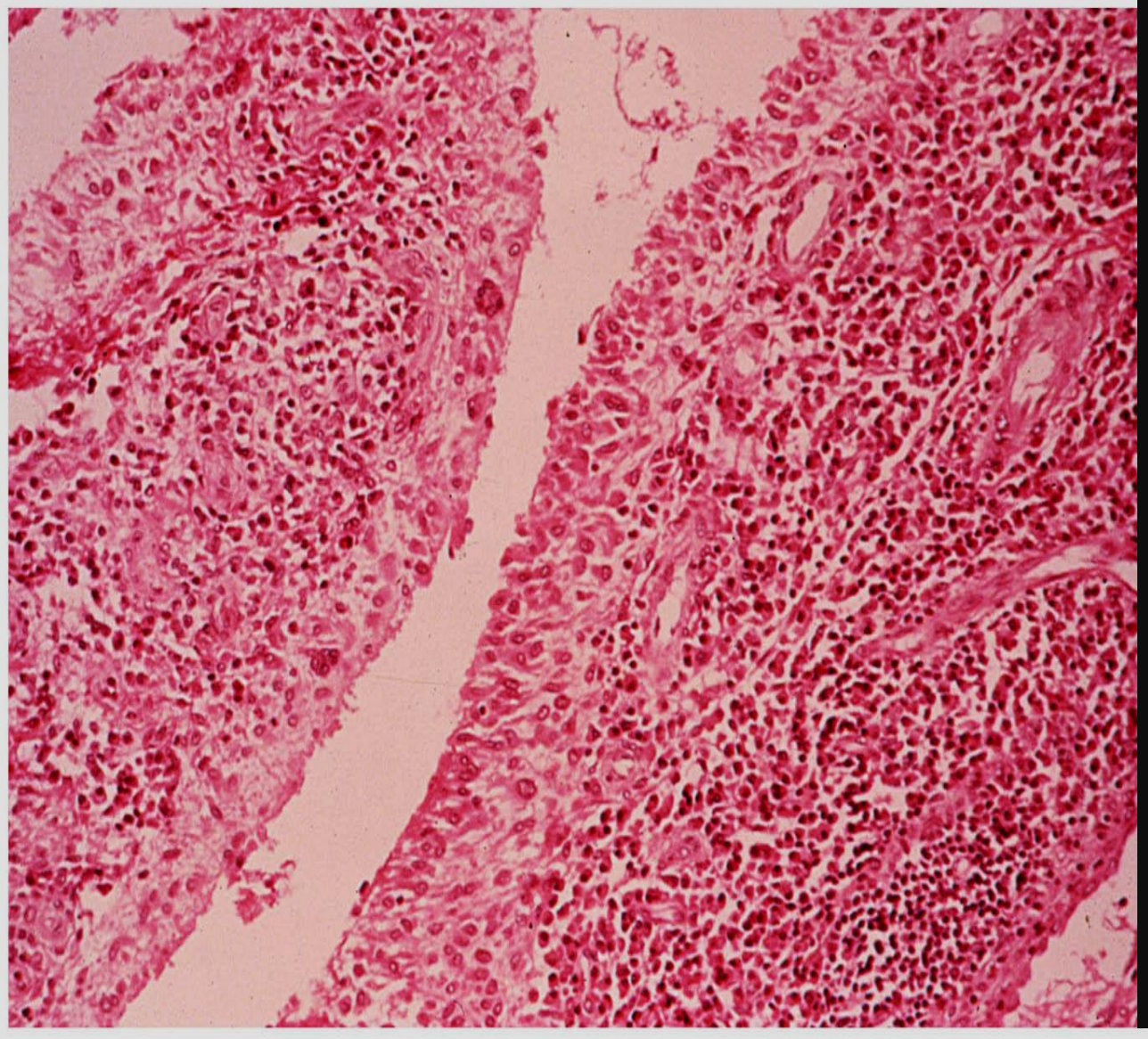
Normal Joint

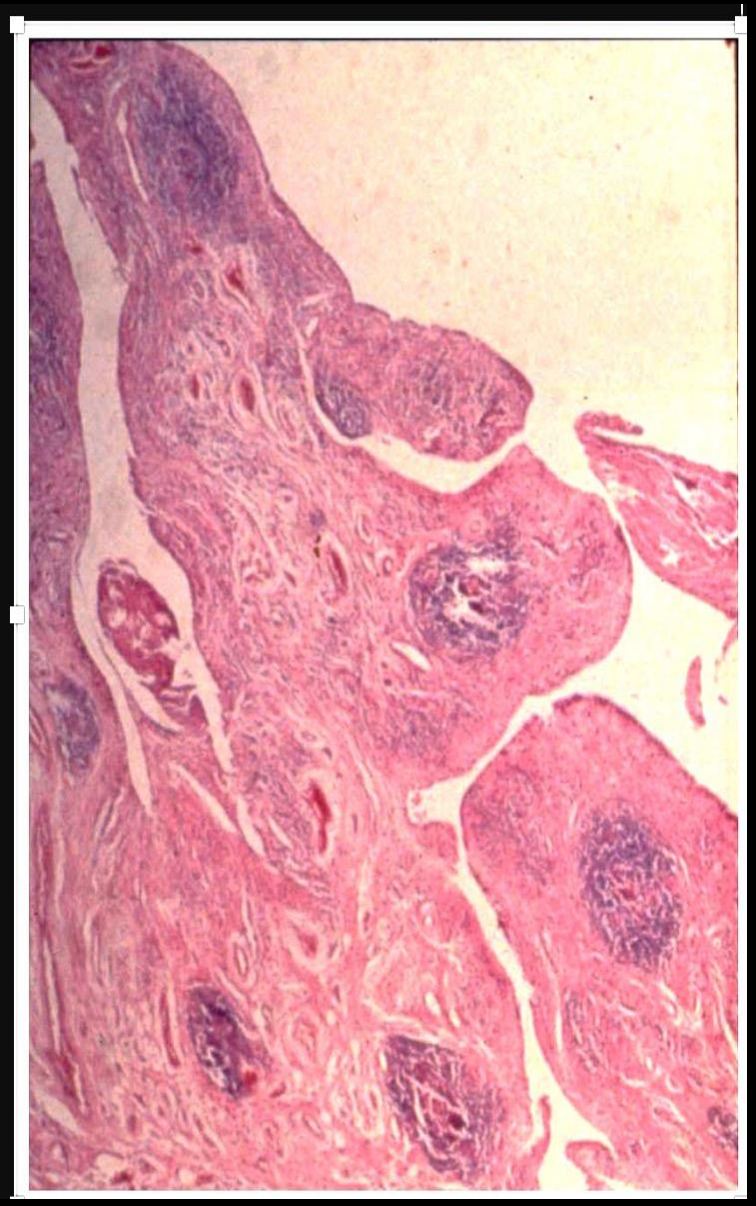


Joint Affected by RA



Adapted from US Department of Health and Human Services Handout on Health. Publication 04-4179.
Slide courtesy of Peng T Fan, MD.



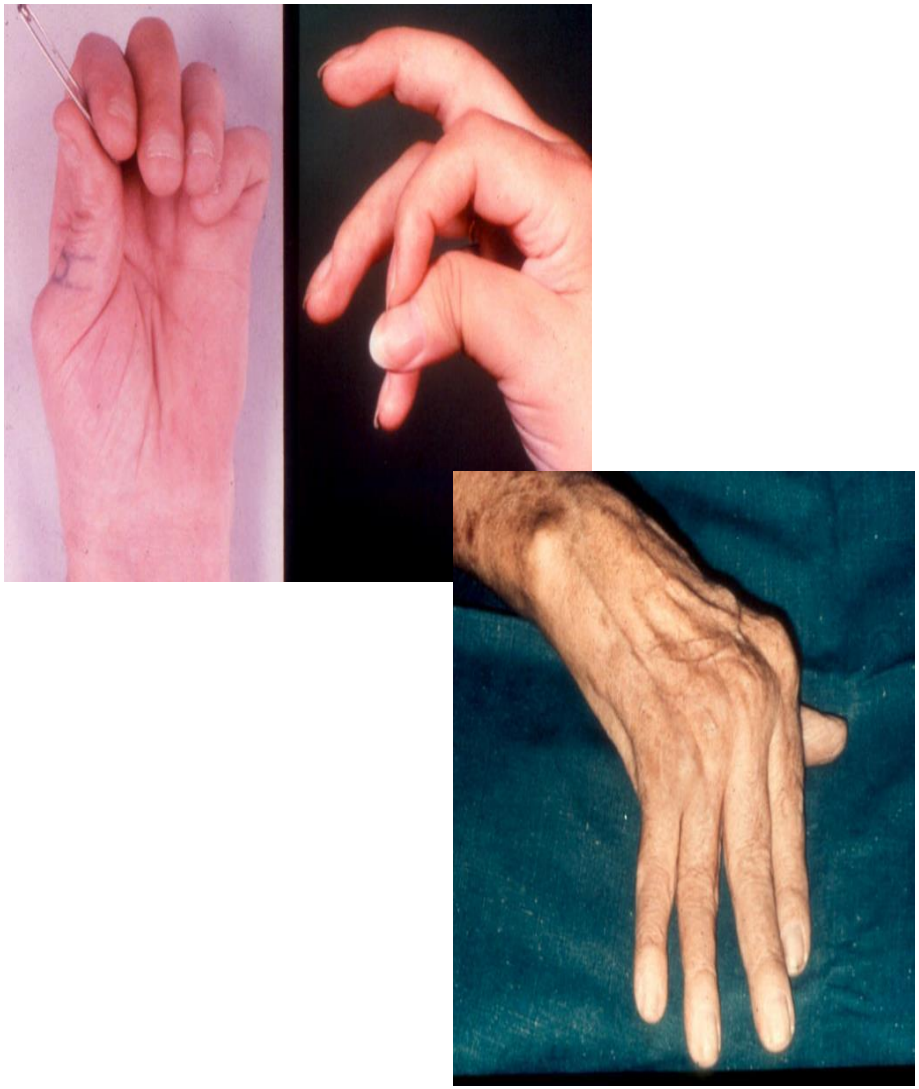


Myeloid vs Lymphoid

Lymphoid Aggregates, B cells, Ectopic Lymph Nodes

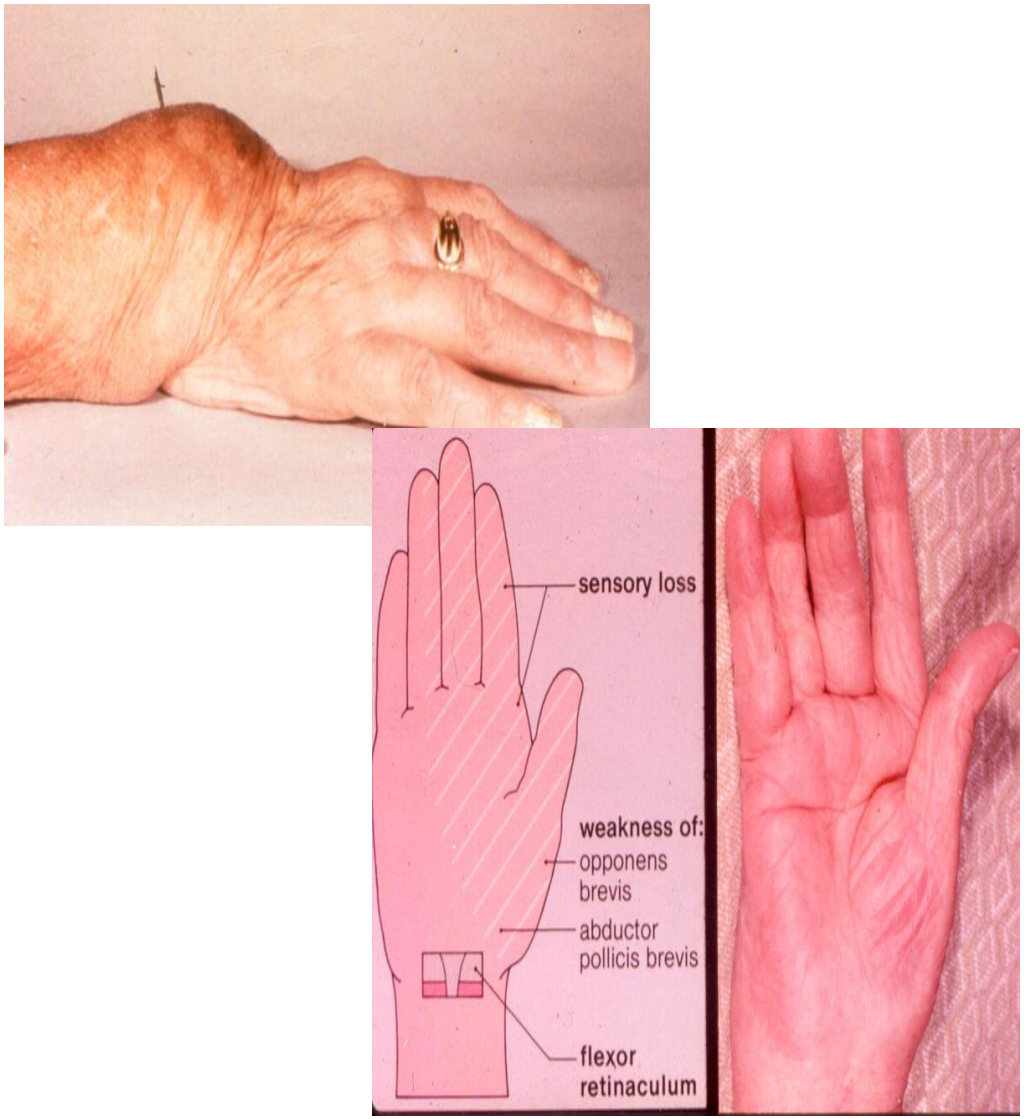
Key Features of RA (Continued)

Hand Deformities



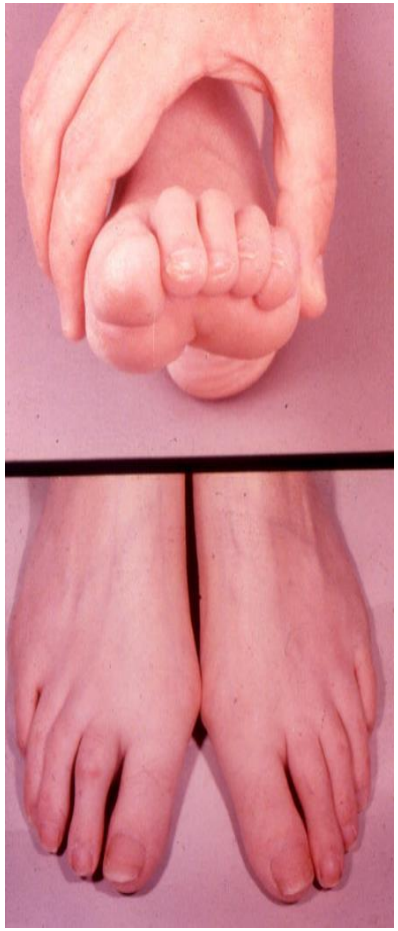
Slide courtesy of Peng T Fan, MD.

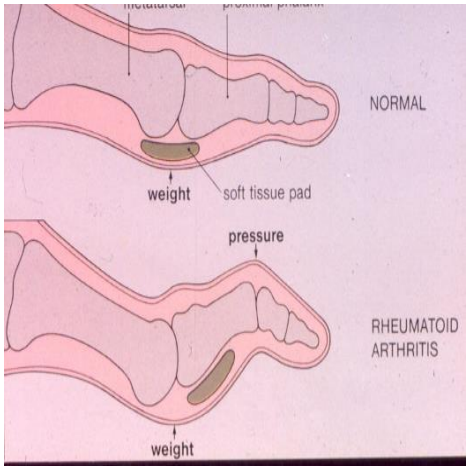
Wrist

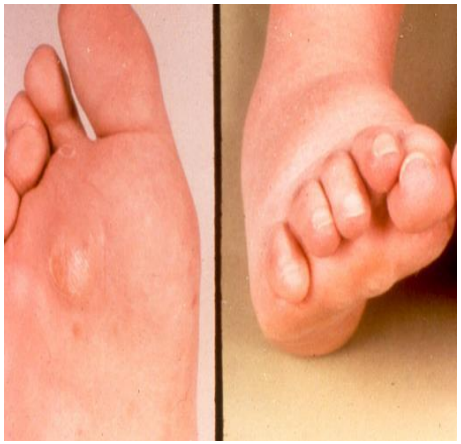


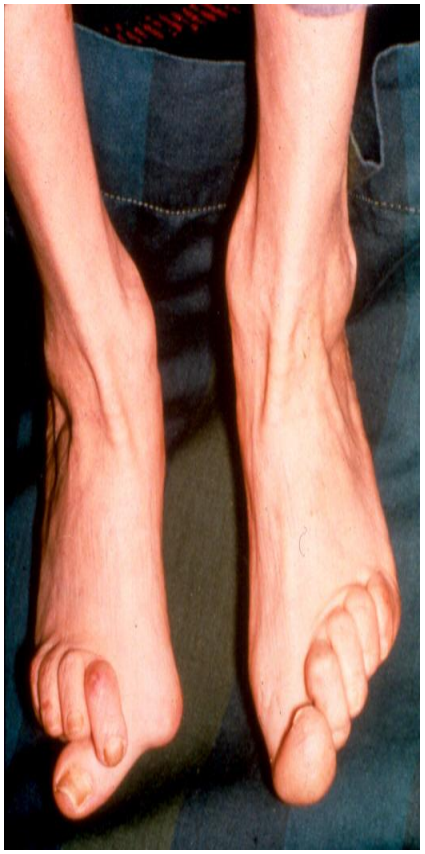
Key Features of RA (Continued)

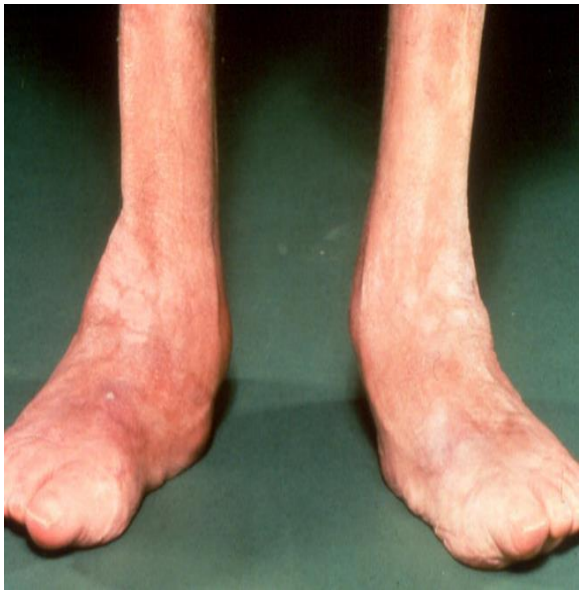
Foot Deformities











Slide courtesy of Peng T Fan, MD.

Laboratory Testing for RA

Rheumatoid Factor (RF)

- Positive predictive value of 28%
- Positive in 5% of general population
- May be negative in RA
- May be negative early and positive later
- Positive in other diseases
- 15% are persistently RF-negative and tend to have milder disease

Anti-CCP Antibody

- More specific assay than RF
- Sensitivity ~ 66.4%, specificity ~ 98.3% (active TB: 7–39%)
- Present in early and preclinical disease (up to 14 years)
- Correlates with increased risk for progressive joint damage
- Does not correlate with fluctuation of RF
- Anti-CCP antibody may be positive in RF-negative patients

Combination of positive RF and anti-CCP in early RA predicts high risk for persistent RA

Raza K, et al. *J Rheumatol*. 2005;32(2):231-238.

Slide courtesy of Peng T Fan, MD.

RA: Seropositive vs Seronegative

Early RA Clinic <6 months Sx

50% seropositive
50% seronegative

Cannot tell difference unless nodules, ILD

"Established" RA-2 years

75% seropositive
25% seronegative

Half of seronegatives remit,never to recur

"Refractory" RA

85% seropositive
15% seronegative

Morbidity, mortality, extra-articular disease in Seropositives>>Seronegatives

Outline:

- RA Overview
- **RA Therapy**
- JAK Inhibitors
- Safety

Targeting Rheumatoid Arthritis

Tolerance broken-AutoAb appear

Adaptive Immunity

Methotrexate/HCQ

Leflunomide

Abatacept

Rituximab

JAK inhibitors

Prednisone

Innate Immunity

TNF-Inhibitors

IL-6-inhibitors

JAK inhibitors

Prednisone

Joint Targeting

Ineffective inhibitors

IL-17

IL12/23

BAFF

IL-1

Tissue Injury

RA Therapy-Section 1

A few slides on Methotrexate until 2025 since it is cheap, easy to take, well-tolerated and it works

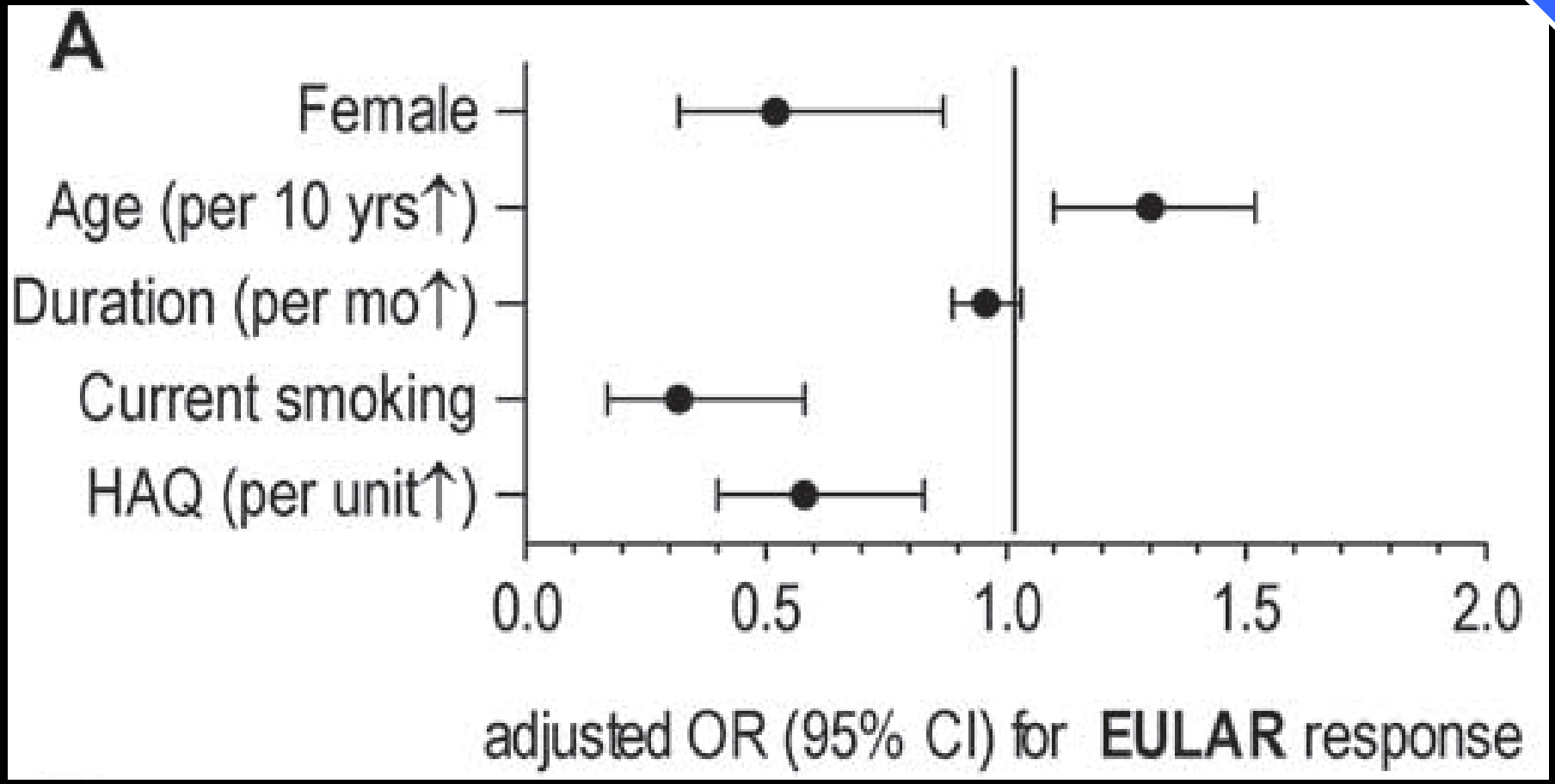
Methotrexate Response

Remission/Low Disease Activity	
LDA (TEAR)	28%
ACR 50 (SWEFOT)	33%
Remission (CATCH)	38% (3 yr)

Long-term data the same
No anti-TNF superior

1. Moreland L et al Arth Rheum 64:2824-35 2012
2. Saevarsdottir S et al. ARD 70: 469 2010
3. Schulman E et al ACR 2015 #3182

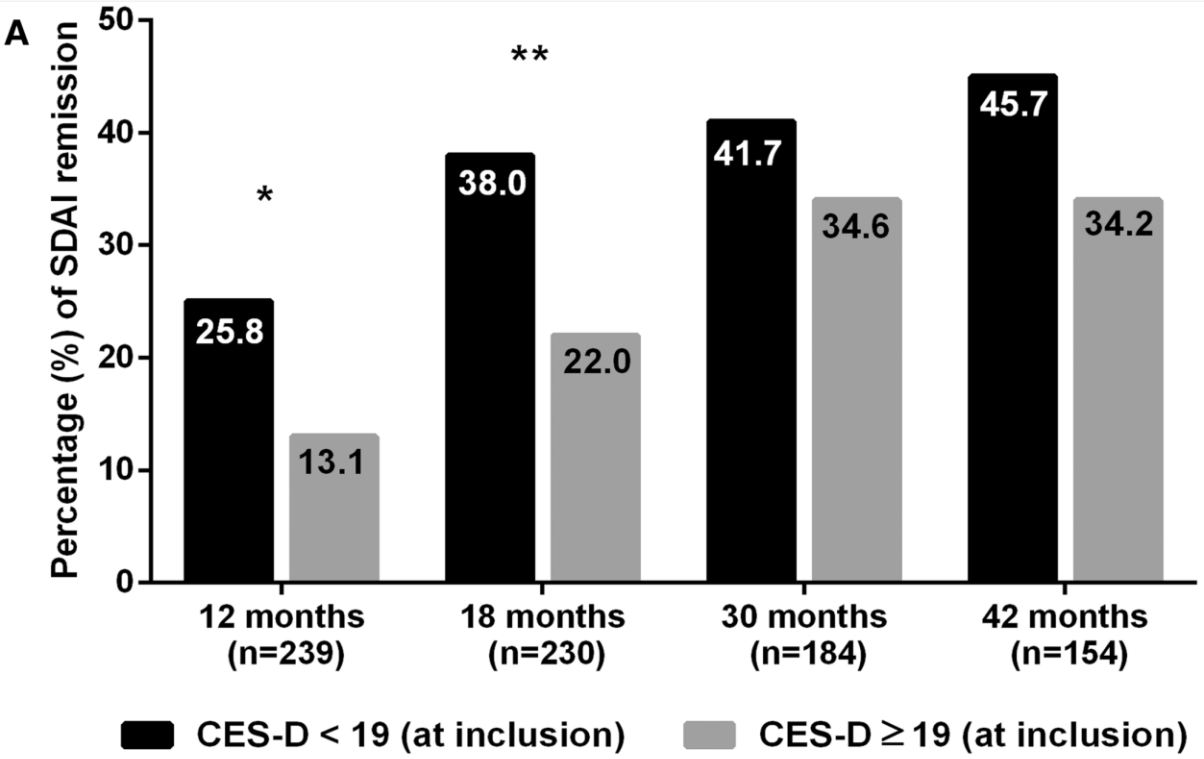
SWEFOT EARLY RA TRIAL: Predictors of MTX Response



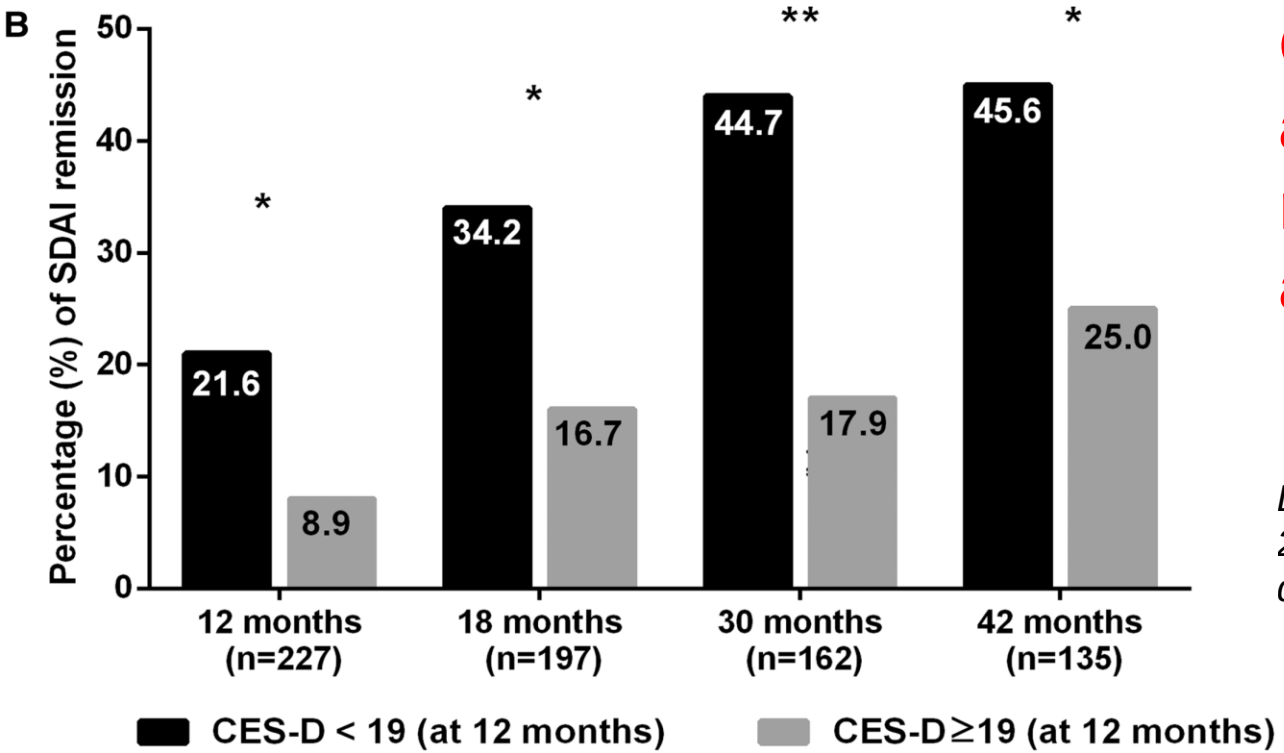
ACPA/RF: No effect

Prednisone 10 mg/d or less (OR 2.84)

Saevarsdottir S et al. ARD 70: 469 2010



Depression as risk factor for non-response

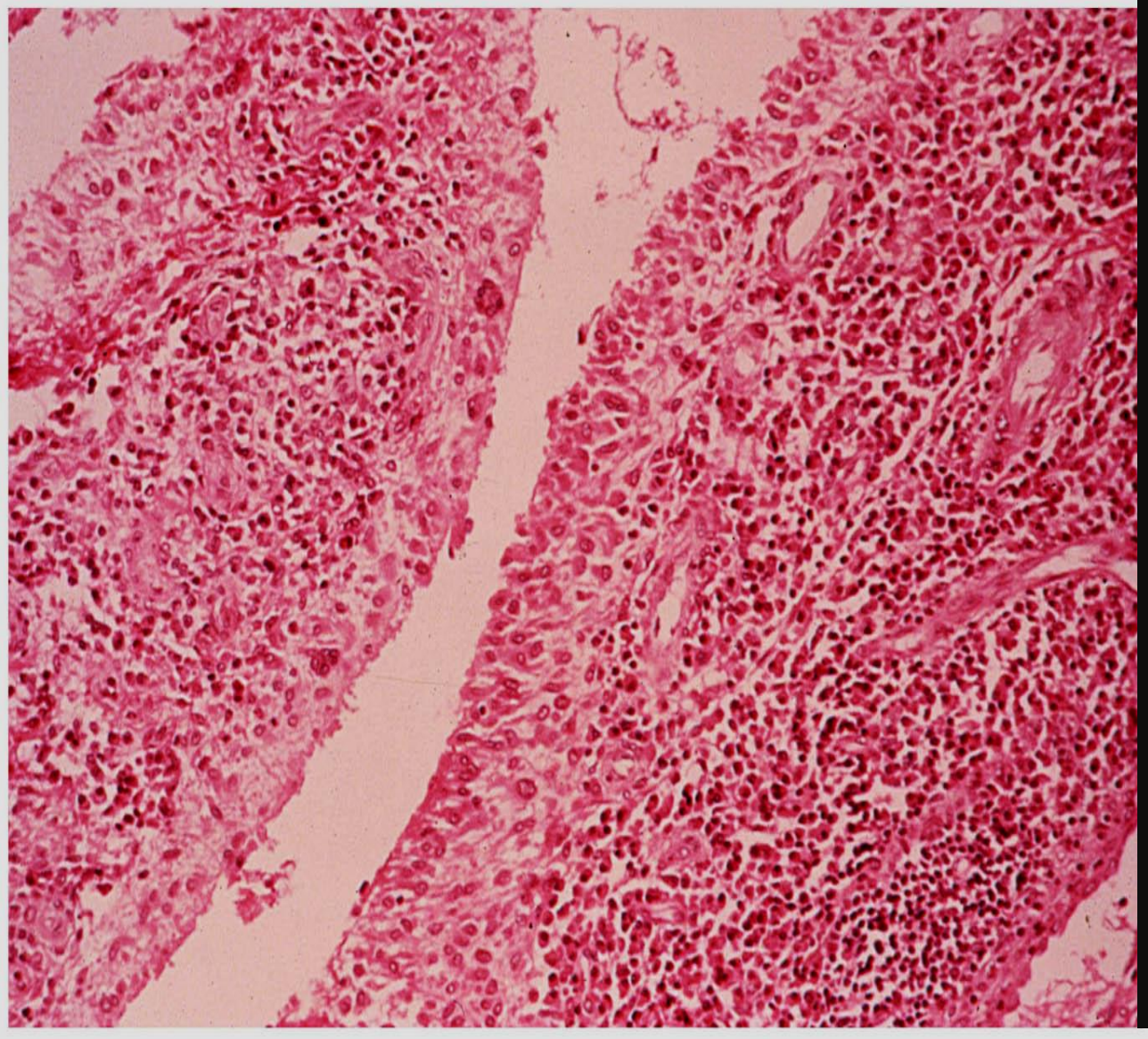


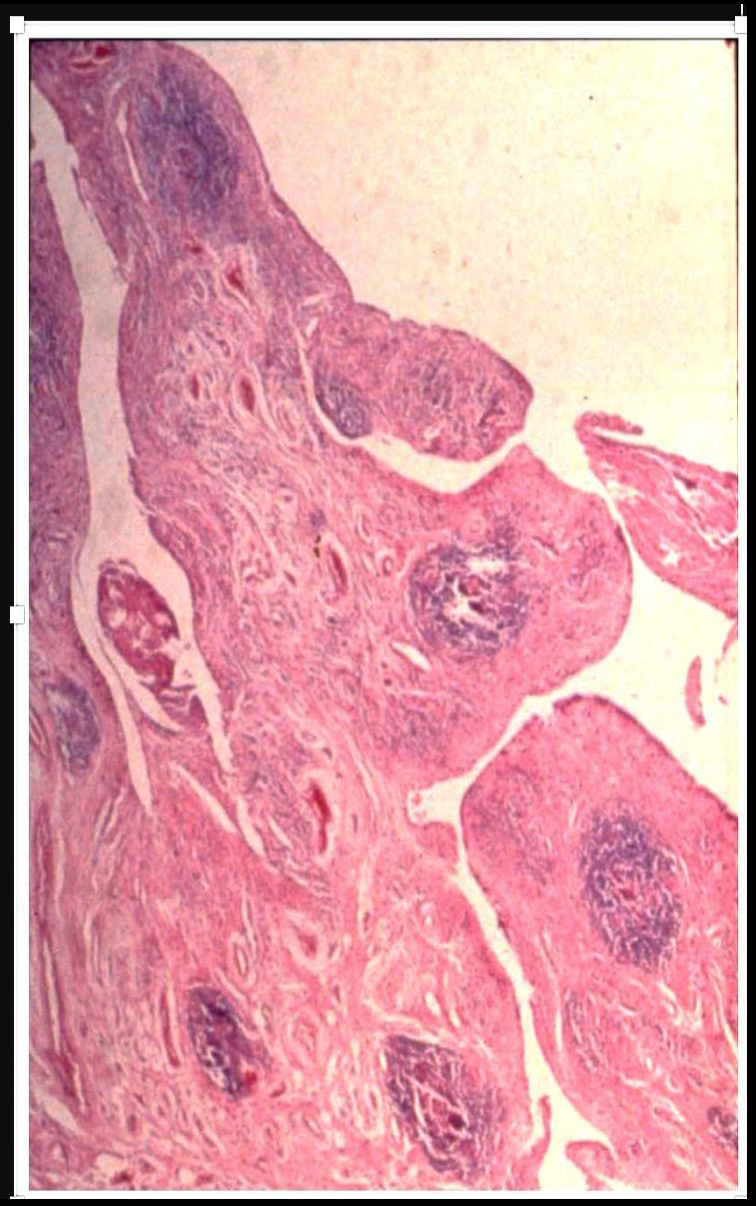
Only depression and BMI affected SDAI remission rates in multivariate analysis

Leblanc-Trudeau C et al. Rheumatology (Oxford). 2015;54(12):2205-2214. doi:10.1093/rheumatology/kev272

RA Therapy-Section 2

What to do after an inadequate response to MTX?

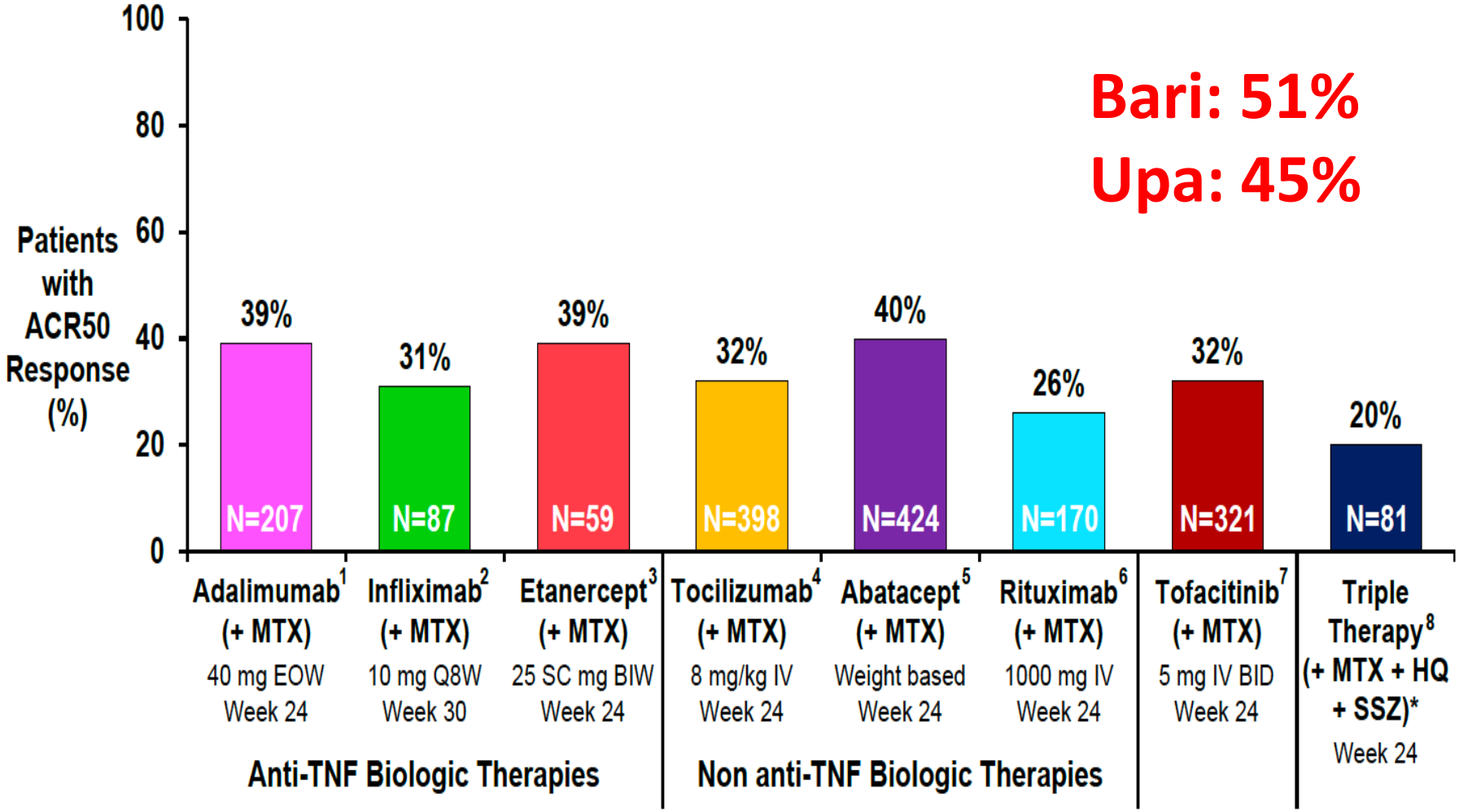




Myeloid vs Lymphoid

Lymphoid Aggregates, B cells, Ectopic Lymph Nodes

Let's Pretend We Can Compare Across MTX-IR Clinical Trials In RA at 12-24 weeks



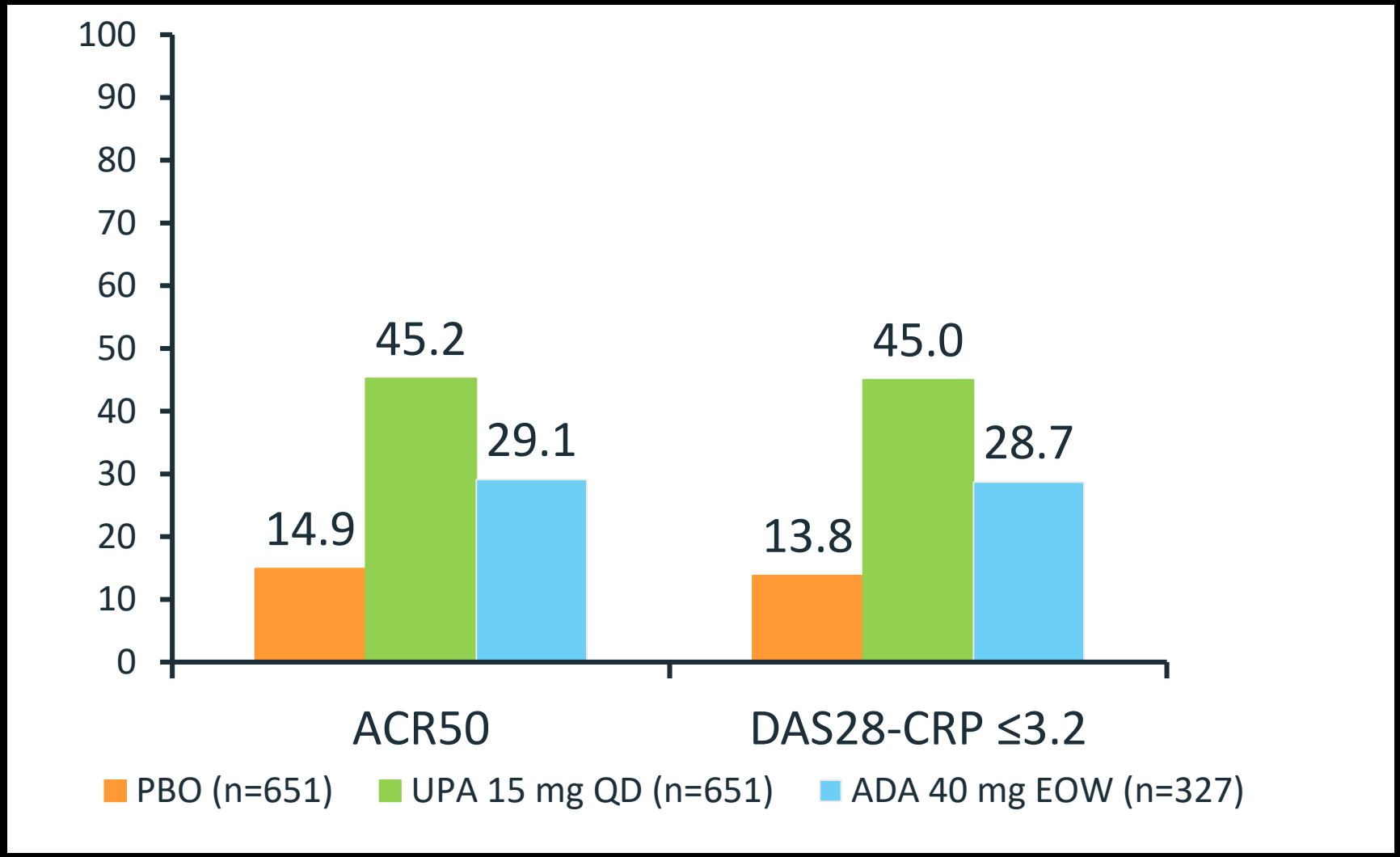
Bari: 51%

Upa: 45%

* MTX=20 mg qw, HCQ=200 mg BID, SSZ=500-1000 mg BID

1-7. USPI, 2018; 8. Moreland, 2012

SELECT-COMPARE: MTX-IR at Week 12
Adalimumab vs. Upadacitinib



Full analysis set
Non responder imputation
***p<0.001, UPA versus PBO

RA Therapy-Section 3

What to do after an inadequate response to a TNF antagonist?

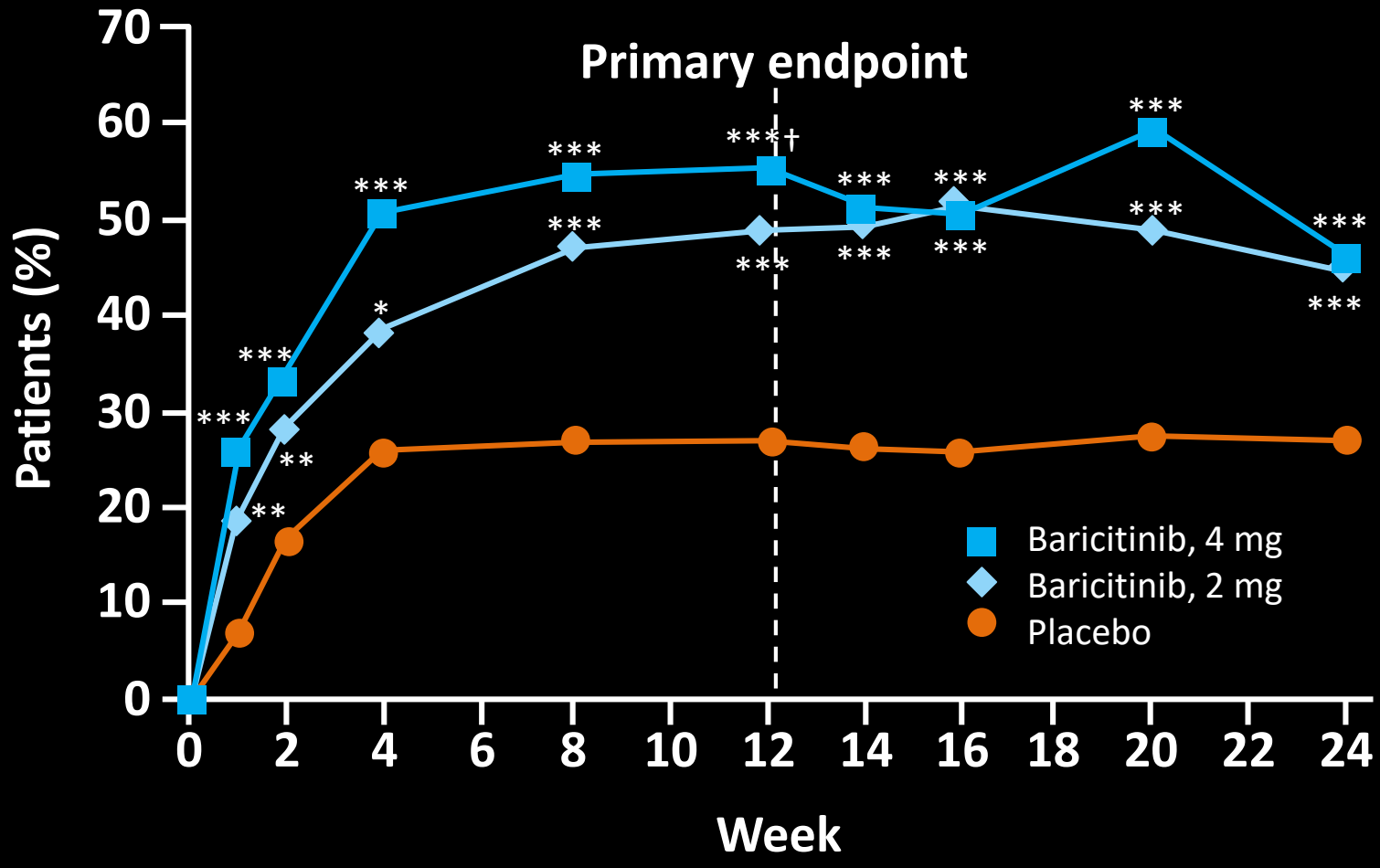
- **RCT parity between biologics**
- **The more biologics you fail the less likely you will respond**

Baricitinib in Biologic-IR RA

Mean disease duration 14 years

TNF IR

ACR20 response



*P≤0.05, **P≤0.01, ***P≤0.001 for supportive analyses comparing baricitinib with placebo, without adjustment for multiple comparisons. †P≤0.001 for comparisons between baricitinib at the 4-mg dose and placebo for the end points of the ACR20 response at week 12, in an analysis that was strongly controlled for multiple comparisons.

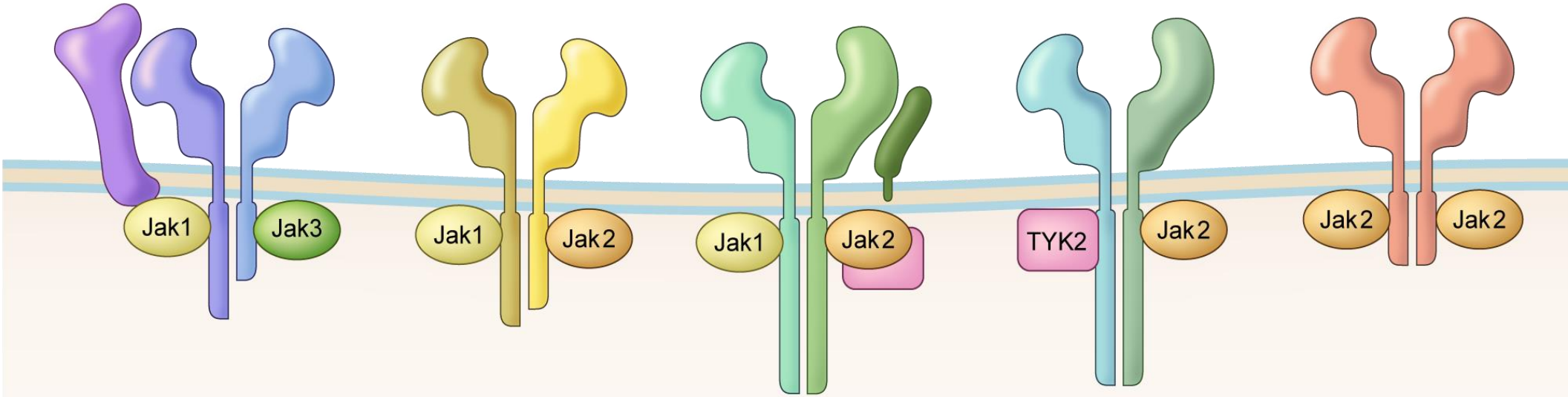
Genovese MC et al. *N Engl J Med.* 2016;374:1243-1252.

Outline:

- RA Overview
- **RA Therapy**
- JAK Inhibitors
- Safety

‘Just another kinase’ 1 & 2
Janus associated kinase

Jaks and Signaling by Type I/II Cytokine Receptors

	γc family IL-2 etc	INF-γ	IL-6 family	IL-12, IL-23	Hormone, Epo, GM-CSF
					
Tofa	+	+	+		
Bari	+	+	+	+	+
Upa	+	+	+		
Filgo	+	+	+		

JAK inhibitor efficacy in RCT

- RA, PsA, AS, GCA, PMR
- **Eczema, alopecia areata, psoriasis**
- **Ulcerative Colitis, Crohns**
- What's next?
  - Soft tissue pain, Fatigue, Bursitis?

Outline:

- RA Overview
- **RA Therapy**
- JAK Inhibitors
- Safety

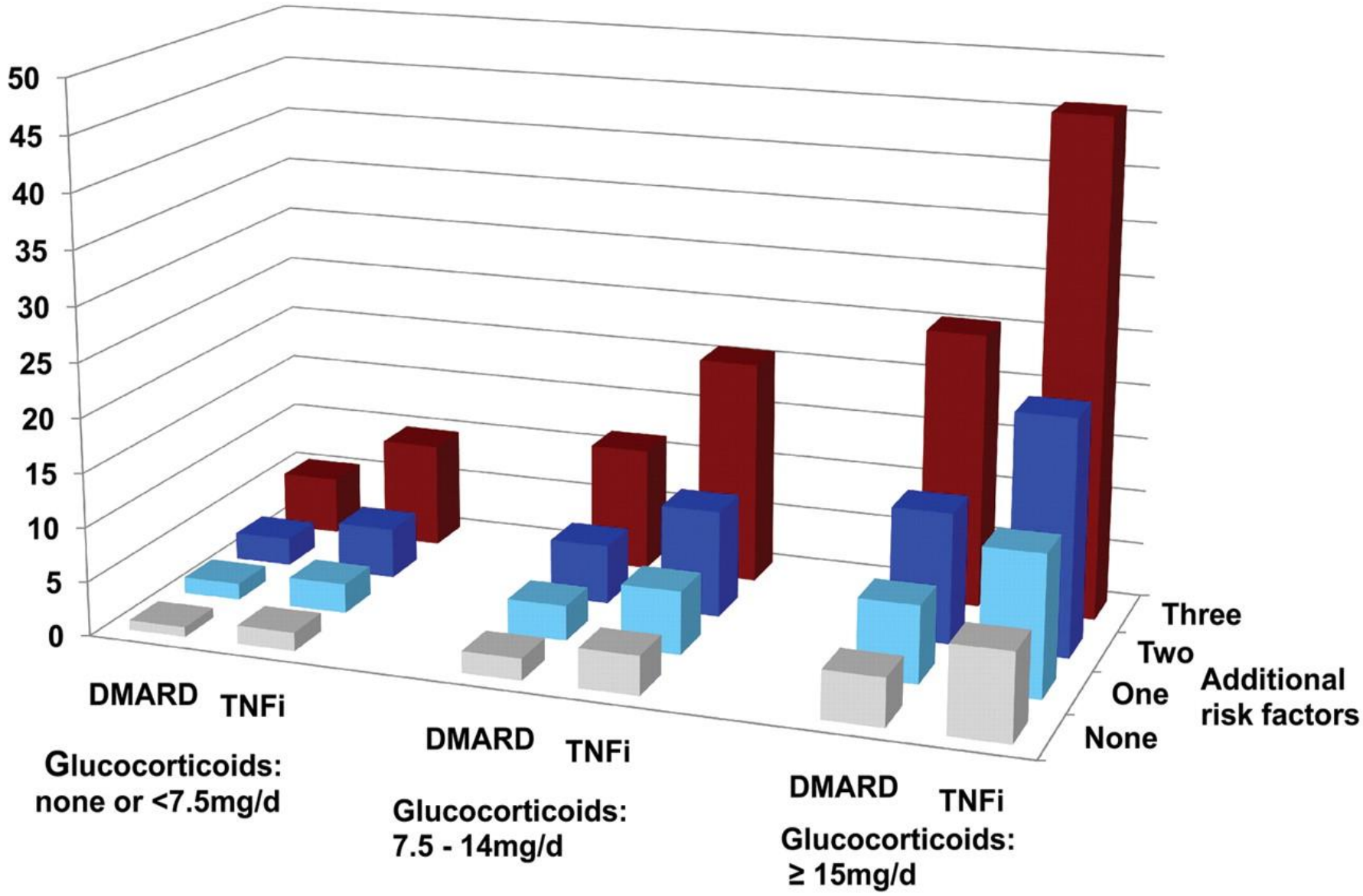
Safety issues rise and fall

Serious Infection rates with biologics HR 1.5-2

Some studies no difference at all-why?

……the power of tapering prednisone

Estimated incidences of serious infections in 100 patients per year by treatment and risk profile.



Strangfeld A et al. Ann Rheum Dis 2011;70:1914-1920

Risk Factors: >60, COPD, CRF, Infection, Functional Status

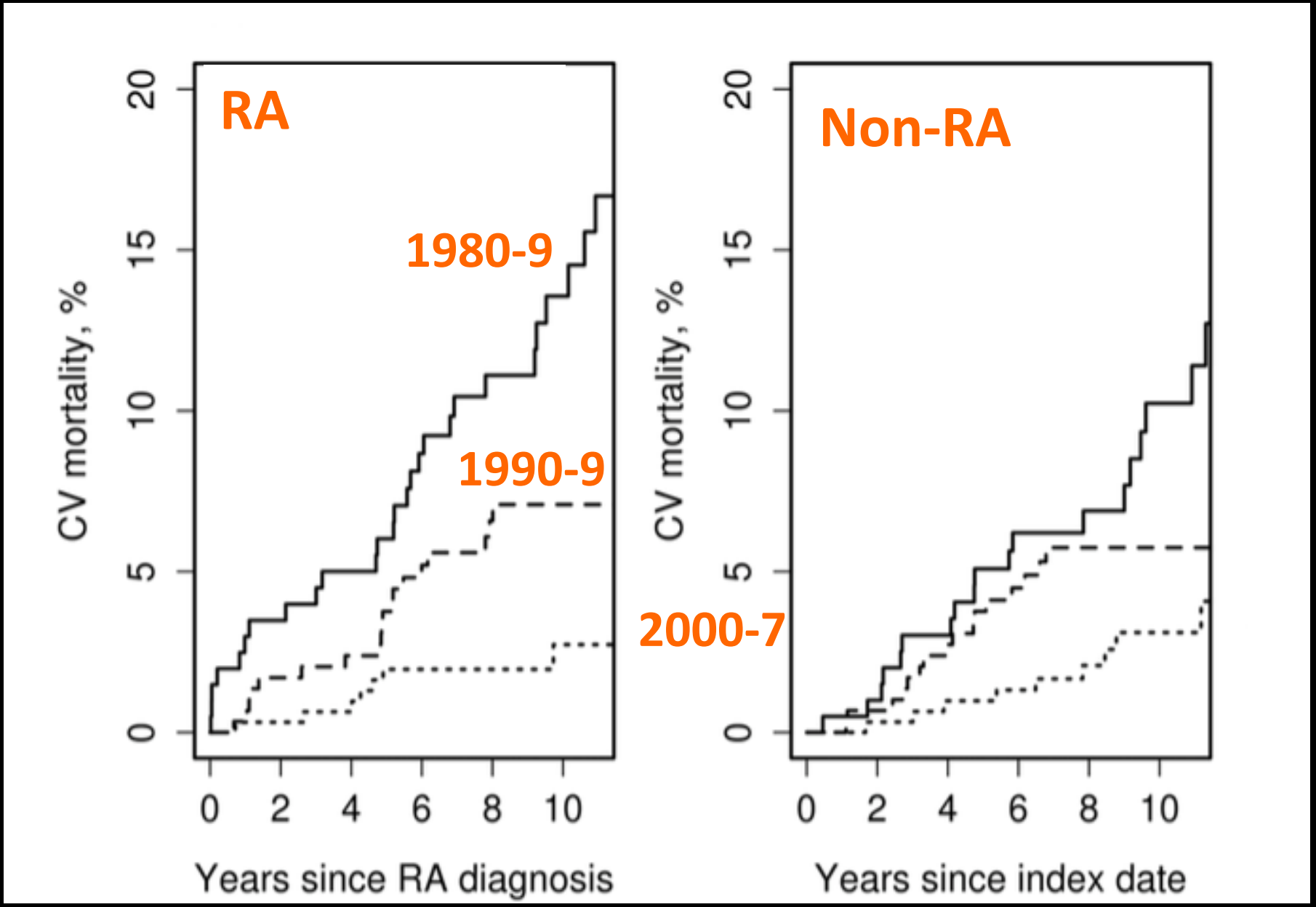
ARD

Safety issues rise and fall

Topics of interest

- Prednisone >10 mg/d
- ASCVD
- Zoster
- Thrombophilia

RA → CV Mortality Disappeared?



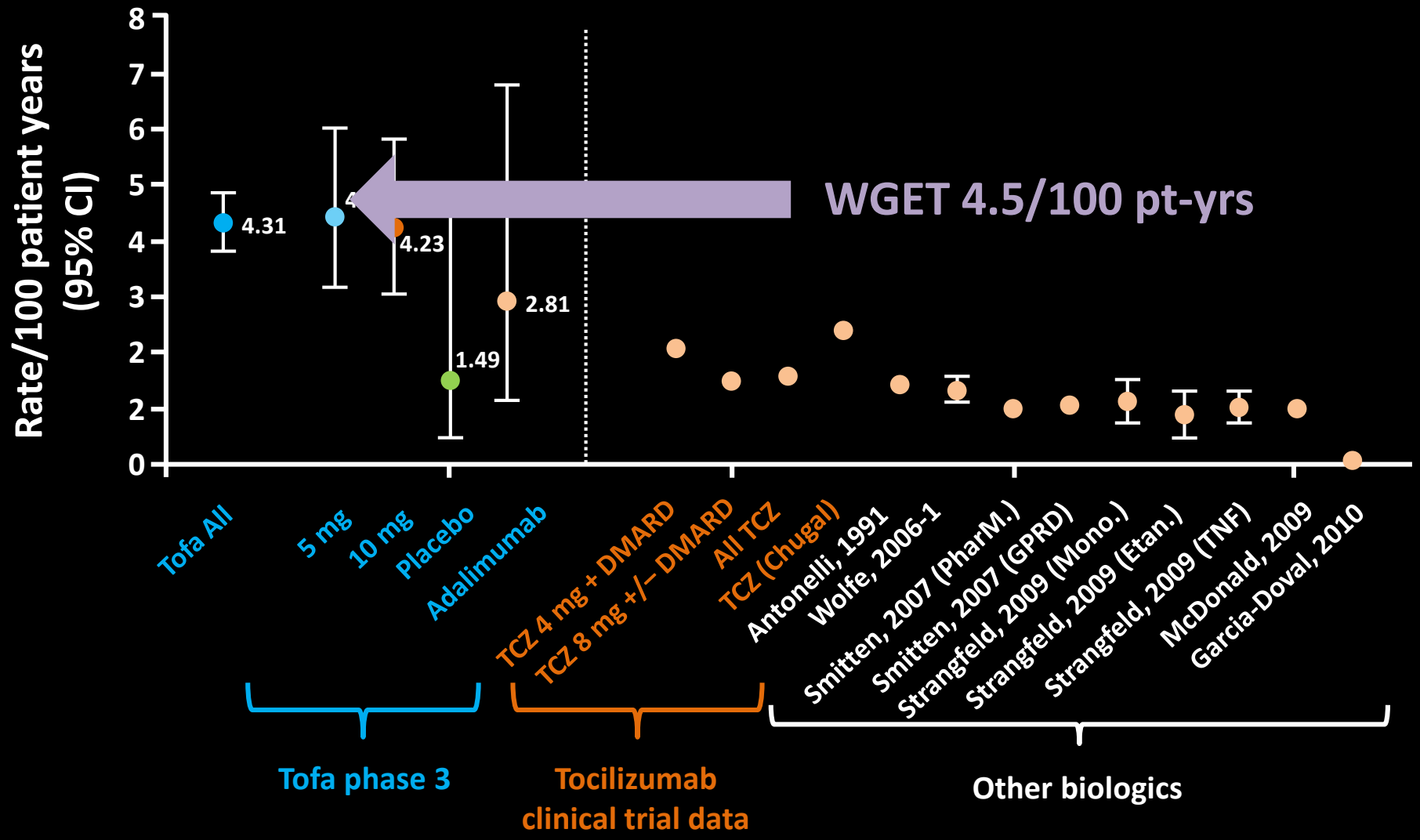
Safety issues rise and fall

Topics of interest

- Prednisone >10 mg/d
- ASCVD
- Zoster
- Thrombophilia

Herpes Zoster Rates in Tofacitinib vs Other Biologics

To date, a class effect



WGET = Wegener's Granulomatosis Etanercept Trial.

2017 knowledge about jakinibs:

Safety not likely to be an issue[1]

6194 patients on tofacitinib (19,406 patient-years)

IR serious infections: 2.7/100 pt-yrs
IR herpes zoster: 3.9/100 pt-yrs ;
IR for GI perforations: 0.1/100 pt-years

SIR for malignancy: <1

1.Cohen SB, et al. Ann Rheum Dis 2017;0:1–10.

VTE and Jakinibs: March 2019

"……the study showed the overall incidence of pulmonary embolism to be 5-fold higher in the tofacitinib 10mg twice daily arm of the study compared with the [tumor necrosis factor] TNF inhibitor arm, and approximately 3-fold higher than tofacitinib in other studies across the tofacitinib program," European Medicines Agency says.

"all-cause mortality in the 10mg twice daily arm in the study was higher than in the 5mg twice daily and TNF-I arms."

VTE and Jakinibs:

- Class Effect re thrombophilia?
  - Filgotinib yet to be besmirched
- If real, mechanism?
  - Rofecoxib or Celecoxib or Troglitazone?

Rare and not so rate events

Rarer events:

IL6 inhibition and diverticular perfs 3/1000 ~HR 2

RTX and PML (1:40,000 patient years)

TNF-I and MS: 1:10,000 patient years

TNF-I and ILD: increased death from ILD

Diabetes and NASH: Hepatotoxicity of MTX, TCZ

Learning Objectives

- **What have we learned about biologics and targeted therapies?**
  - **Highly effective agents exist**
  - **Cost the biggest barrier** until 2025?

Learning Objectives

What about these meds will make your patient's day?

The need for these agents is well-defined

Efficacy measures and predictors are clear

Lifestyle (weight loss, tobacco cessation) provide clear yields

Learning Objectives

- **What about these meds will ruin your patient's day (and yours)? What do I need to be vigilant about?**
  - **Prednisone dose**
  - **Recurrent infection typically sinopulmonary**
  - **Rare side effects**
  - **Efficacy of Zoster vaccination studies**

Thank you! Questions?

Does Seropositivity Predict Outcomes?

No evidence for differential with ETN/INF[1,2]

RF Differential: **Rituximab (OR 5.0)**

TCZ OR increased by RF 1.5X not ACPA[3-5]

No data: Tofacitinib

1. *Hyrich KL et al. Arthritis Rheum. 2007;56:13-20.*
2. *Potter C et al. Ann Rheum Dis. 2009:68:69-74.*
3. *Maneiro R et al. Sem Arth Rheum 43: 9-13 2013*
4. *Lal P et al. Arthritis Rheum. 2011;63:3681-3691.*
5. *Cappelli LC et al Sem. Arth Rheum 2017 (in press)*

Four Questions in RA Pathophysiology

What to do with a seropositive individual without symptoms, mild symptoms, or intermittent symptoms (e.g., PR) and no findings?

How does systemic autoimmunity (ACPA) become synovial autoimmunity?

When does it become RA?

How is RA related to lung and cardiovascular comorbidities?

PR = palindromic rheumatism

Polling QuestioN

You have a patient with positive ACPA without symptoms.

What is the likelihood of RA in 3 years?

A. <5%

B. <10%

C. <20%

D. <30%

E. <50%

F. >60%

The Likelihood of RA with Positive ACPA Results

Diagnostic Accuracy of ACPA in the General Population

- Serum from Swedish twin cohort (n = 12,590)
- 350 of 12,590 individuals had positive anti-CCP2 test
- 103 had RA diagnosis at blood donation (29.4%)
- 21/247 (8.5%) developed RA in over 3 years

Diagnostic Accuracy of ACPA in Patients with Lung Disease

- 33 high titer ACPA positive patients w/ILD
- 3 (9%) → RA with median follow up 449 days

Fischer A, et al. *Respir Med*. 2012;106:1040-1047; Hensvold AH, et al. *Ann Rheum Dis*. 2017;76(1):119-125.

Polling QuestioN

You are seeing a 35-year-old woman with ACPA and/or RF+ with peri-menstrual arthralgias. What is the likelihood of RA in 1 year?

A. <5%

B. <10%

C. <20%

D. <30%

E. <50%

F. >60%

Seropositivity with Arthralgia

147 seropositive patients with arthralgia. 50 ACPA, 52 RF, 45 double positive:

- 29/147 (20%)→polyarthritis in over 28 months
- 26/95 (ACPA+ACPA/RF) = ~27% (<14%/year)
- 26/29 who progressed were ACPA+ = 90%
- 3/52 (6%) with isolated RF ~<3%/year

Bos WH, et al. *Ann Rheum Disease.* 2010;69(3):490-494.