

Rheumatoid Arthritis: When to Start and when to Stop anti-TNF Therapy

[¿Cuando iniciar o detener
la tx anti-TNF?]

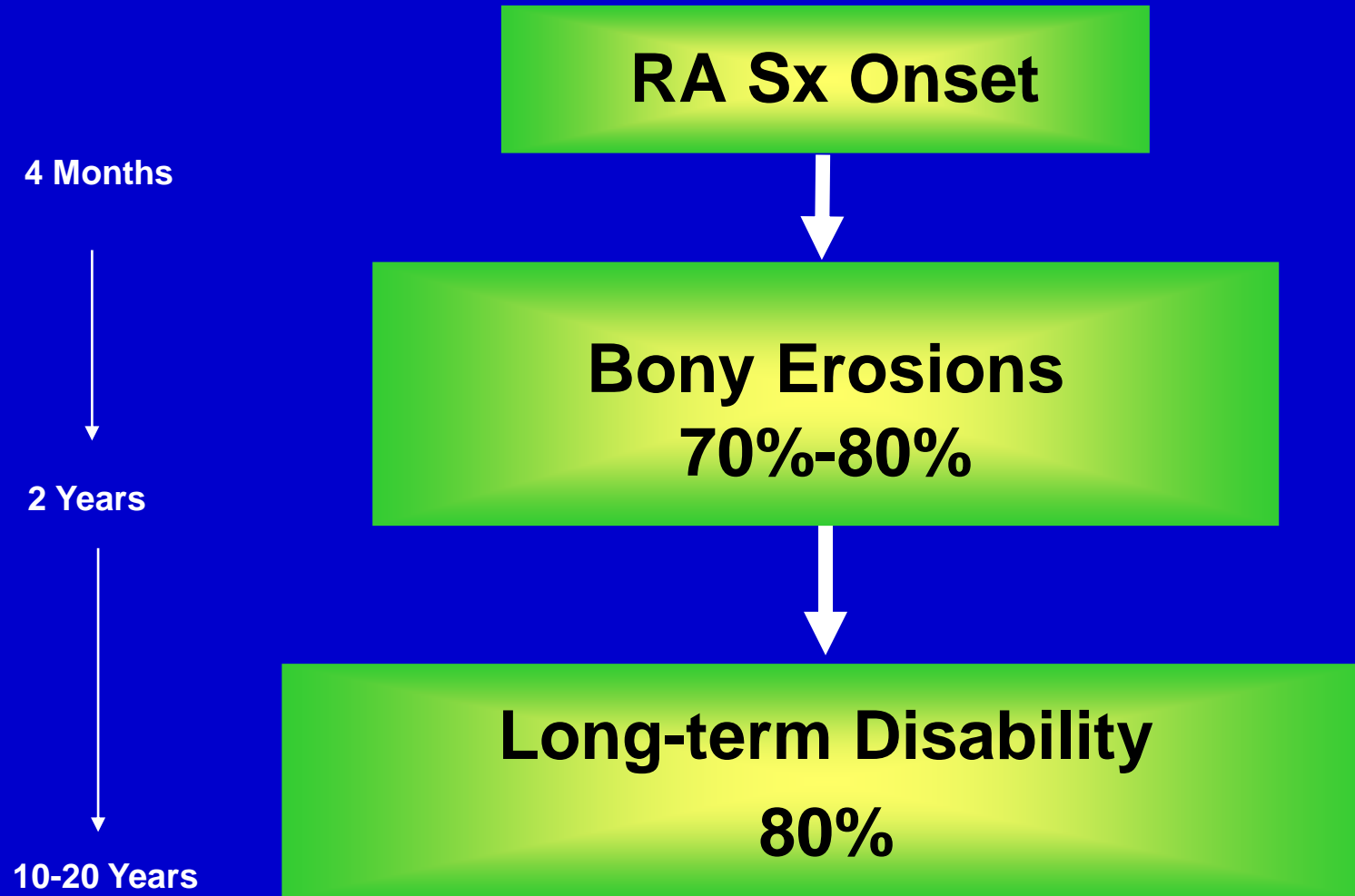
Asociacion Costatarricense Medicina Interna
August 7, 2015

Arthur Weinstein, MD, FACP, FRCP, MACR
Professor of Medicine, Georgetown University
Rheumatology, MedStar Washington Hospital Center

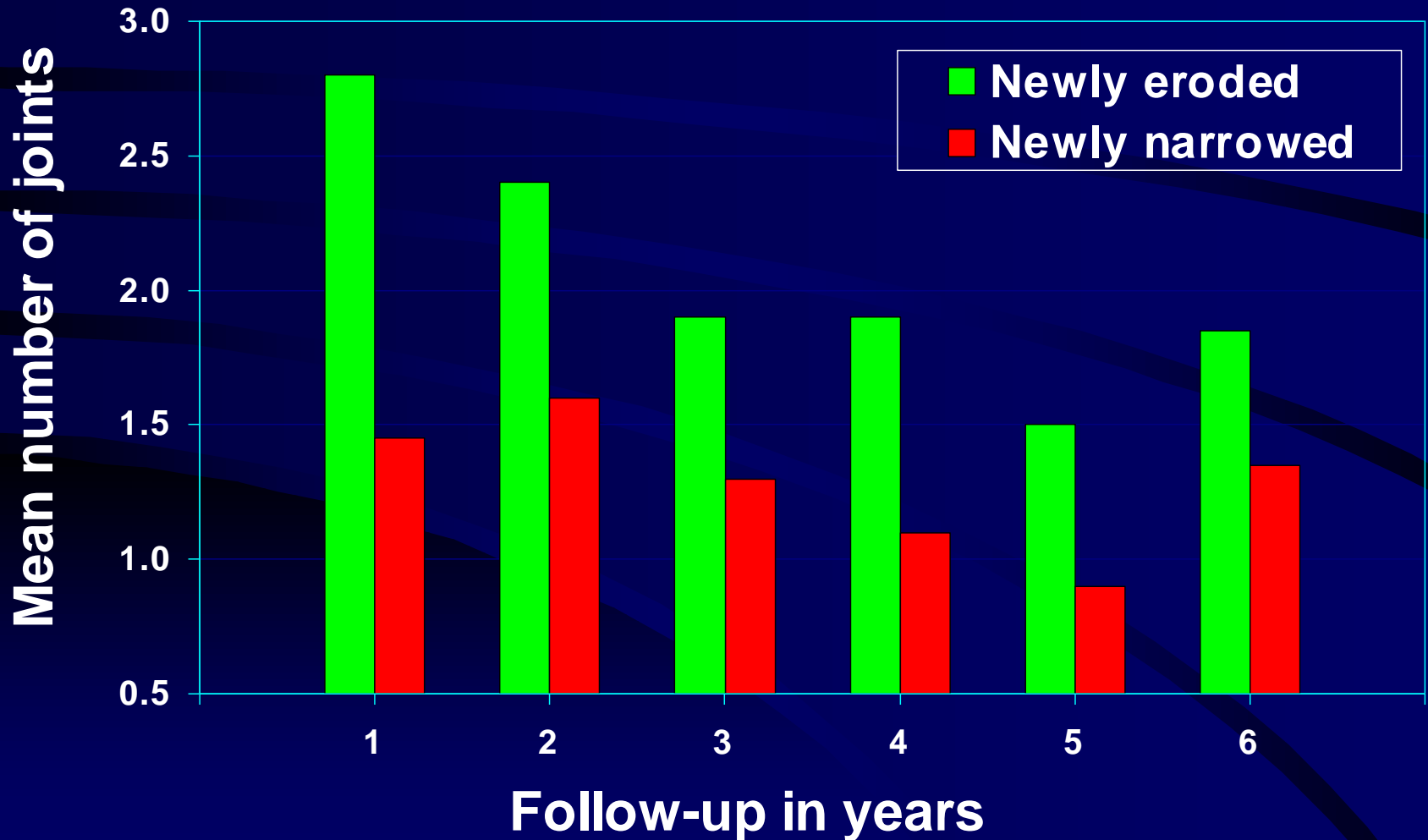
Progression of RA



Rheumatoid Arthritis (RA): The Window of Treatment Opportunity

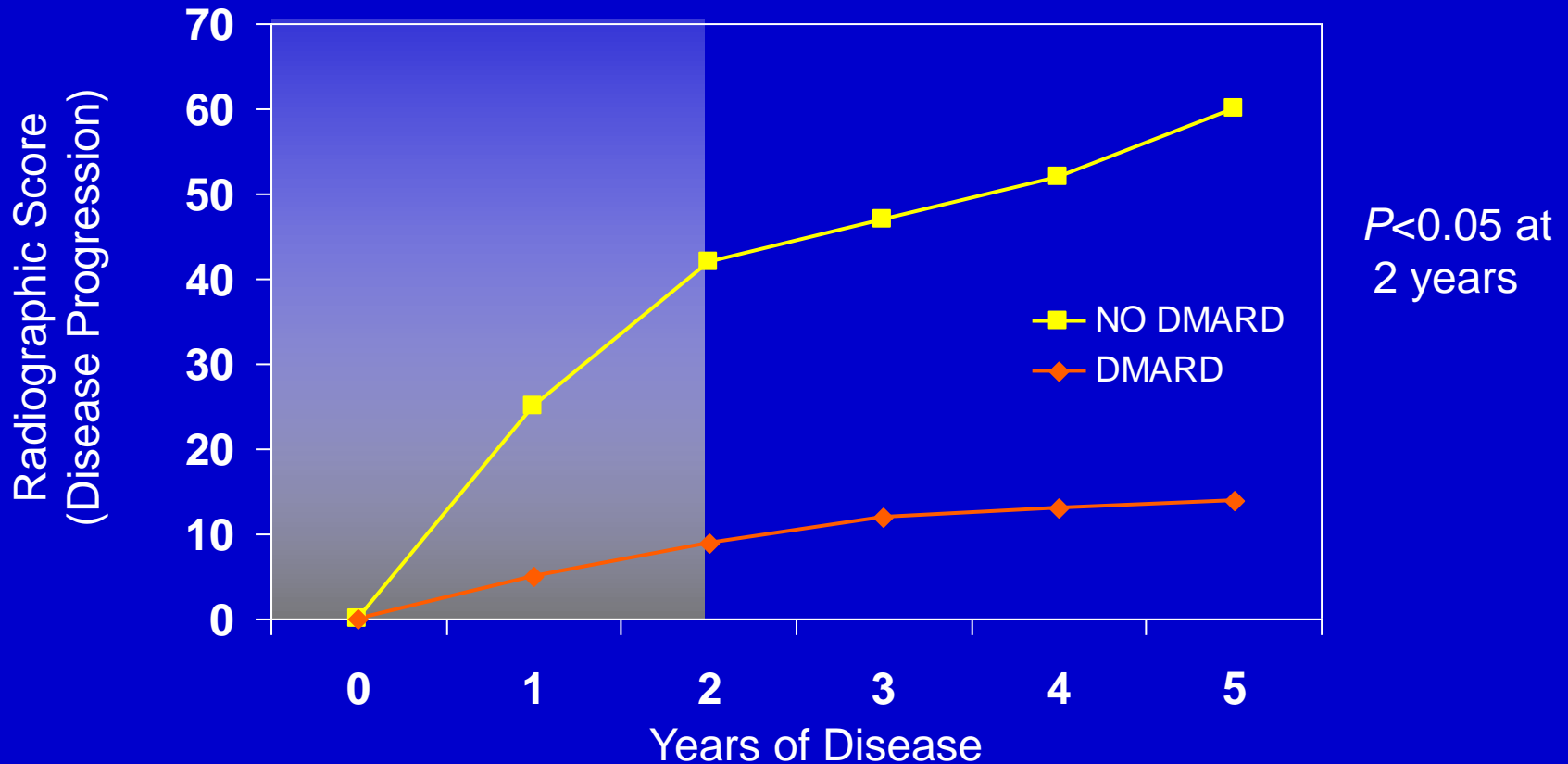


Rate of Development of New Damage of Joints



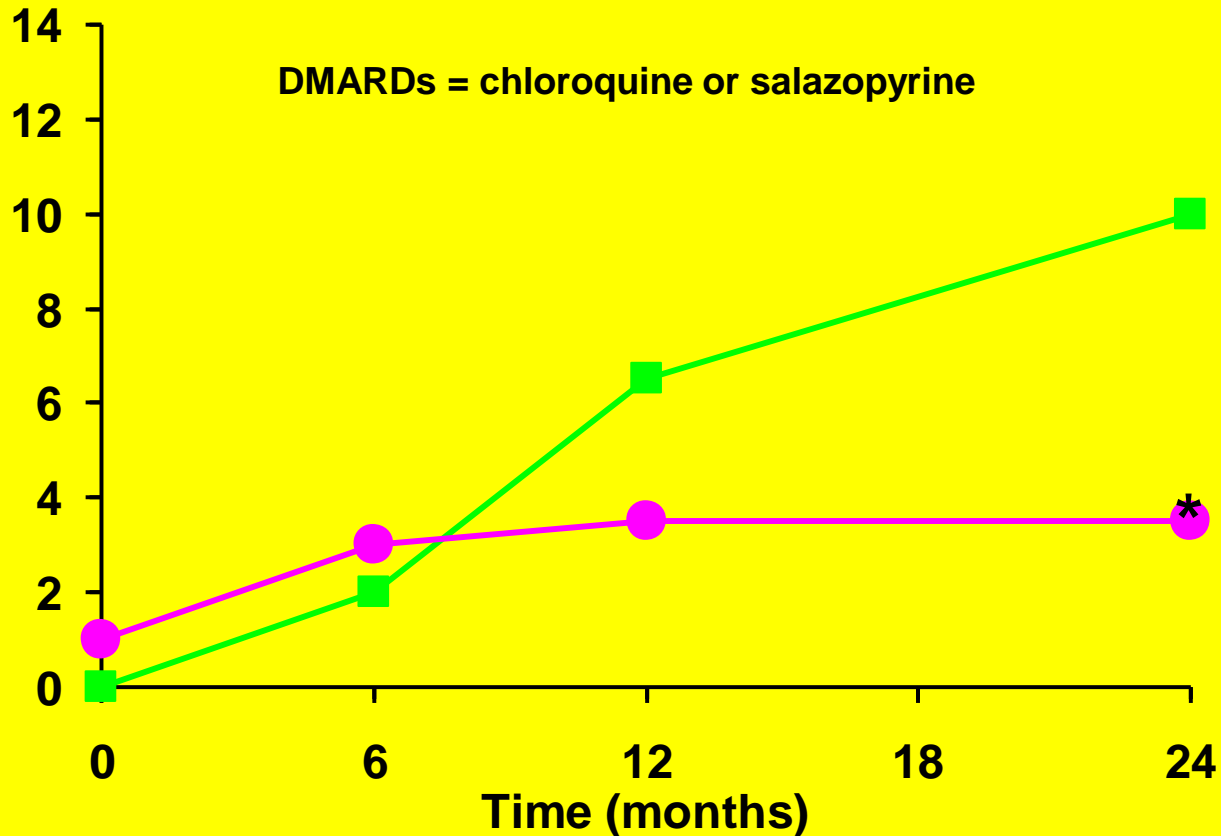
Window of Opportunity in RA: Disease Modifying anti-rheumatic Drugs (DMARDs)

DMARDs are associated with a decrease in radiographic progression



DMARD Treatment: The Earlier the Better

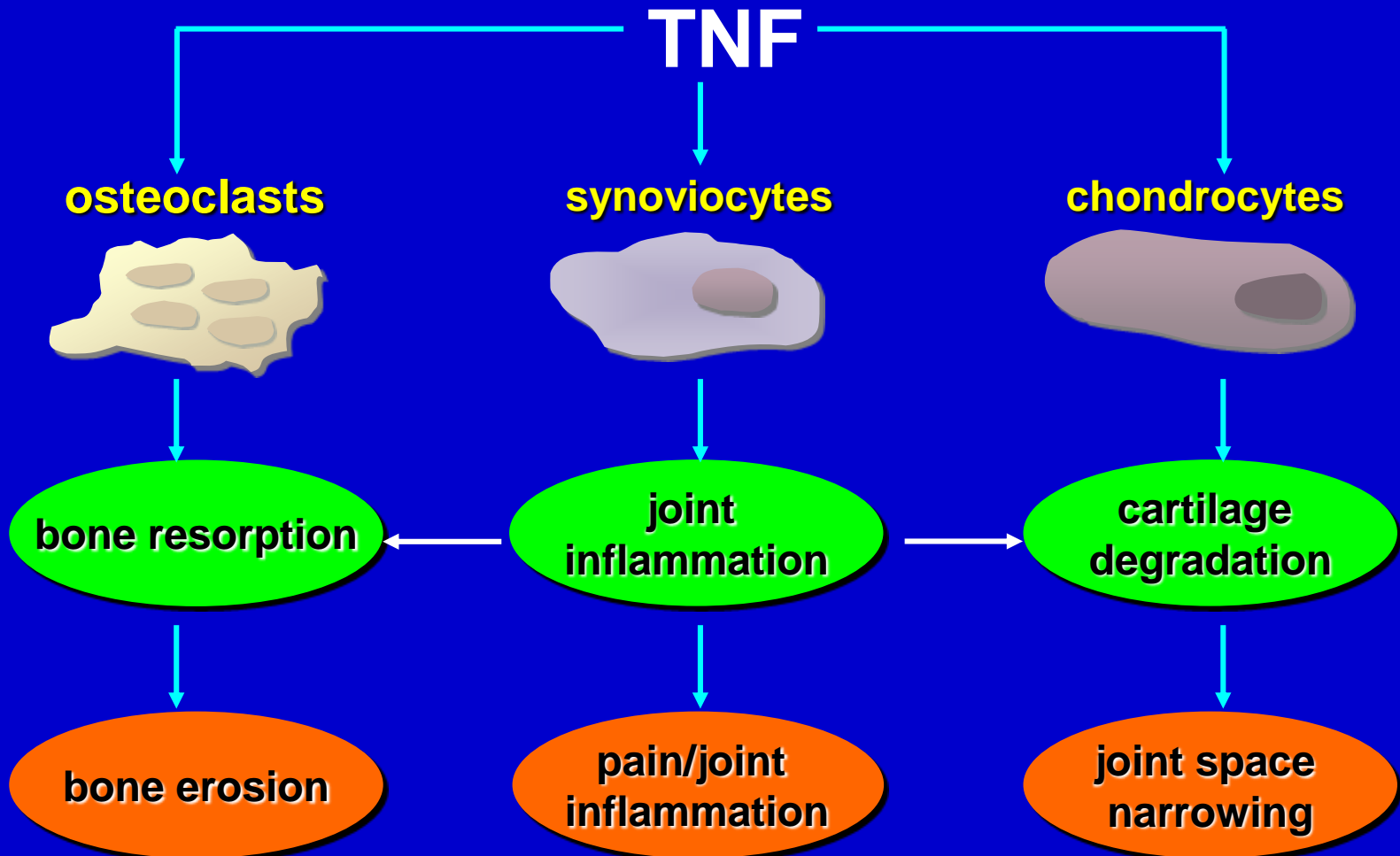
- Delayed treatment (median treatment lag time, 123 days; n = 109)
- Early treatment (median treatment lag time, 15 days; n = 97)



*p < 0.05 vs delayed-treatment group.

Lard LR et al. *Am J Med.* 2001;111:446-451

Central Role of TNF in RA



TNF Antagonists

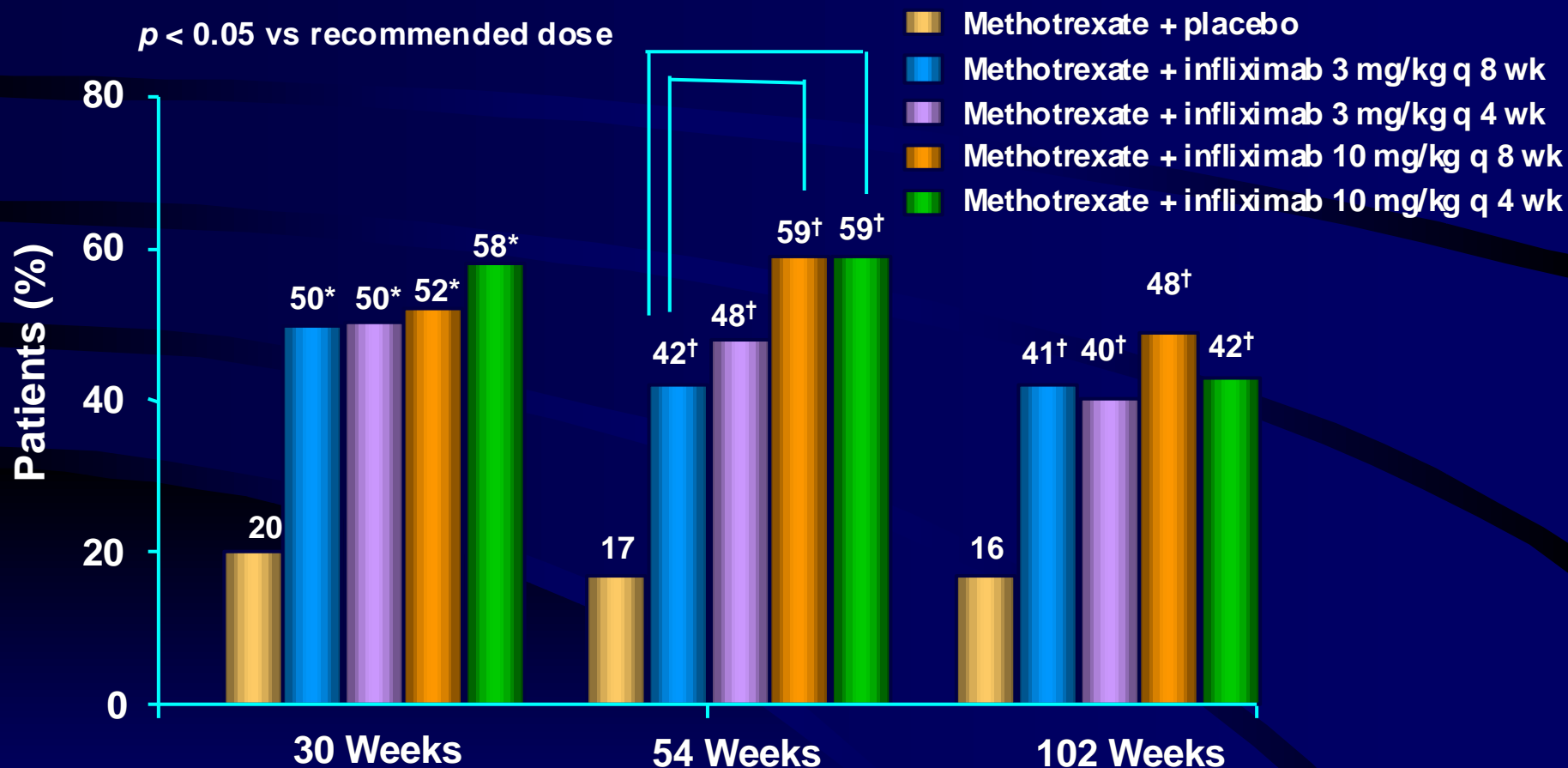
- 5 currently approved agents (USA):
 - etanercept, adalimumab, infliximab, certolizumab pegol, golimumab
- Subcutaneous (etanercept, adalimumab, certolizumab pegol, golimumab) and intravenous administration (infliximab)
- Administration in combination with MTX is superior to monotherapy*
- Time to onset: rapid (weeks)
- **Adverse events**
 - infection - bacterial, TB, fungal, H. Zoster
 - malignancy - not higher rates than the background of lymphoma and solid tumors in RA population
 - multiple sclerosis/demyelination, lupus-like syndrome, worsening CHF, ?Hep B reactivation syndrome (esp infliximab)
- **Monitoring**
 - TB screening including PPD prior to therapy, Hep B screenig
 - Periodic CBC, LFTs
 - Infection

O'Dell JR. *N Engl J Med.* 2004;350:2591-2602.

Klareskog L, et al *Lancet.* 2004;363:675-681*; Breedveld F, et al. *Arthritis Rheum.* 2006;54:26-37*.

ACR20 Response

Infliximab/ Methotrexate Combination (ATTRACT)

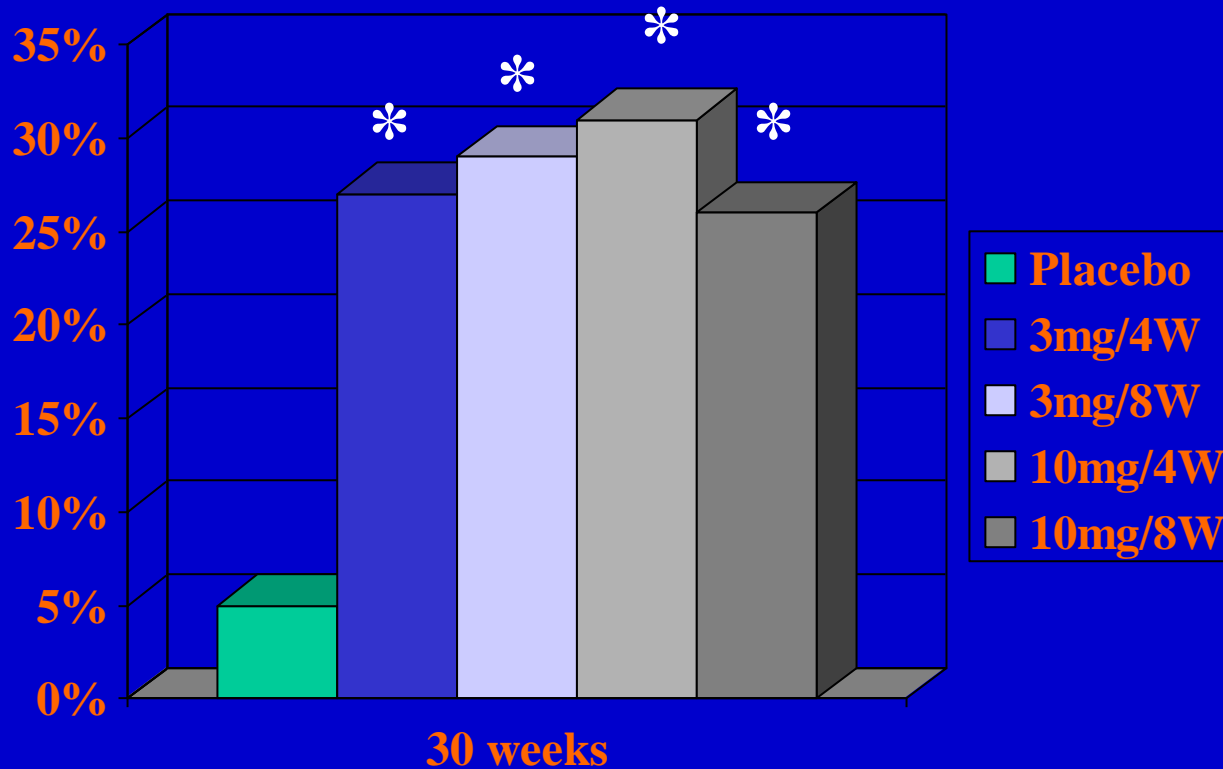


* $p < 0.001$ vs control
† $p < 0.05$ vs control

Maini. *Lancet*. 1999.
Lipsky. *Arthritis Rheum*. 1999.
Lipsky. *Arthritis Rheum*. 2000.

ATTRACT STUDY GROUP

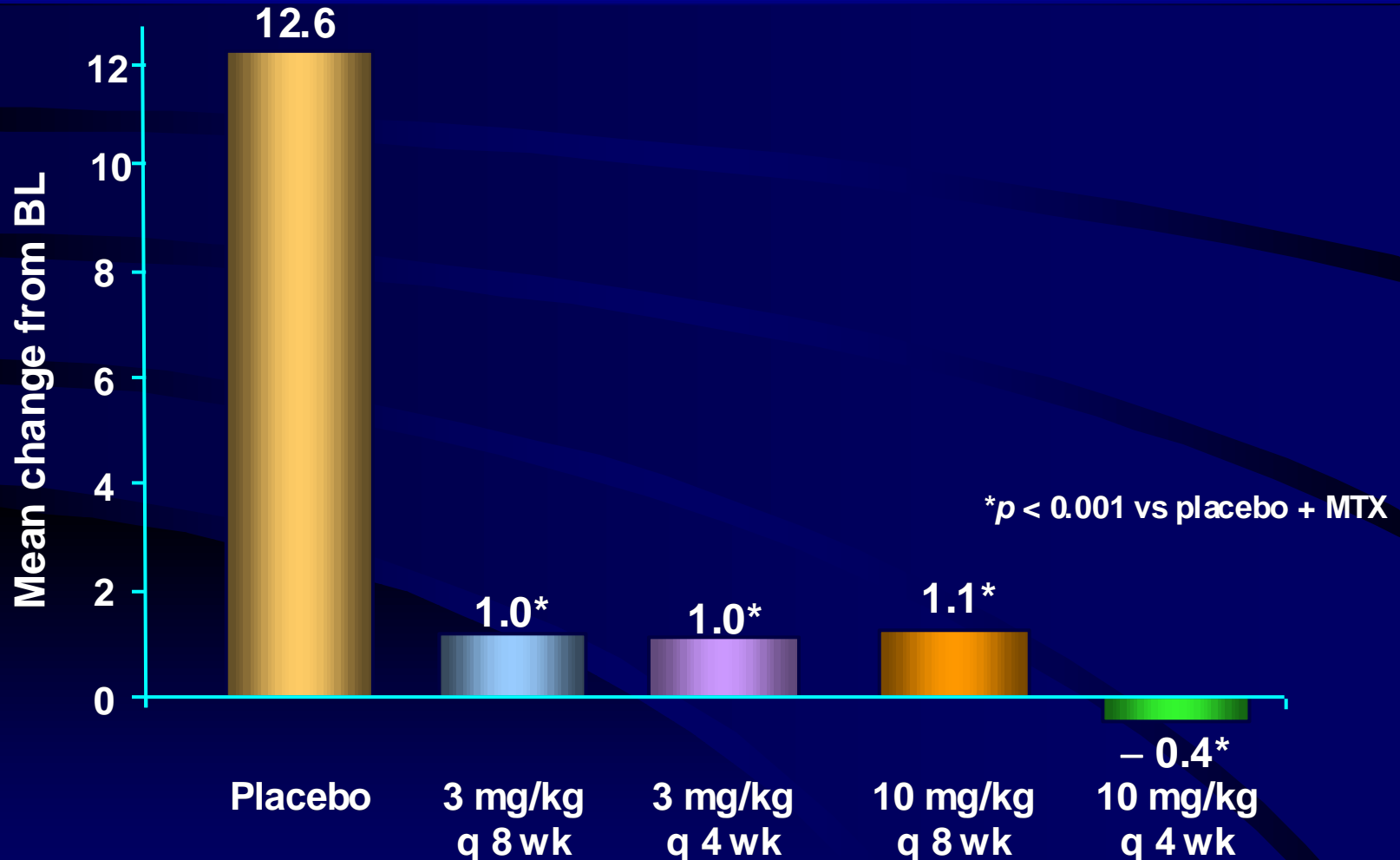
PERCENTAGE OF PATIENTS THAT REACHED ACR 50



* P<0.001

ATTRACT Trial

Mean Change in Total Modified Sharp Score at Week 102



Other biologics and small molecule for RA

- Abatacept (Orencia) – recombinant CTLA4-Ig (co-stimulatory blockade)
- Rituximab (Rituxan) – B-cell depletion (anti-CD20)
- Tocilizumab (Actemra) – IL-6 receptor antagonist
- Anakinra (Kineret) – recombinant IL-1 receptor

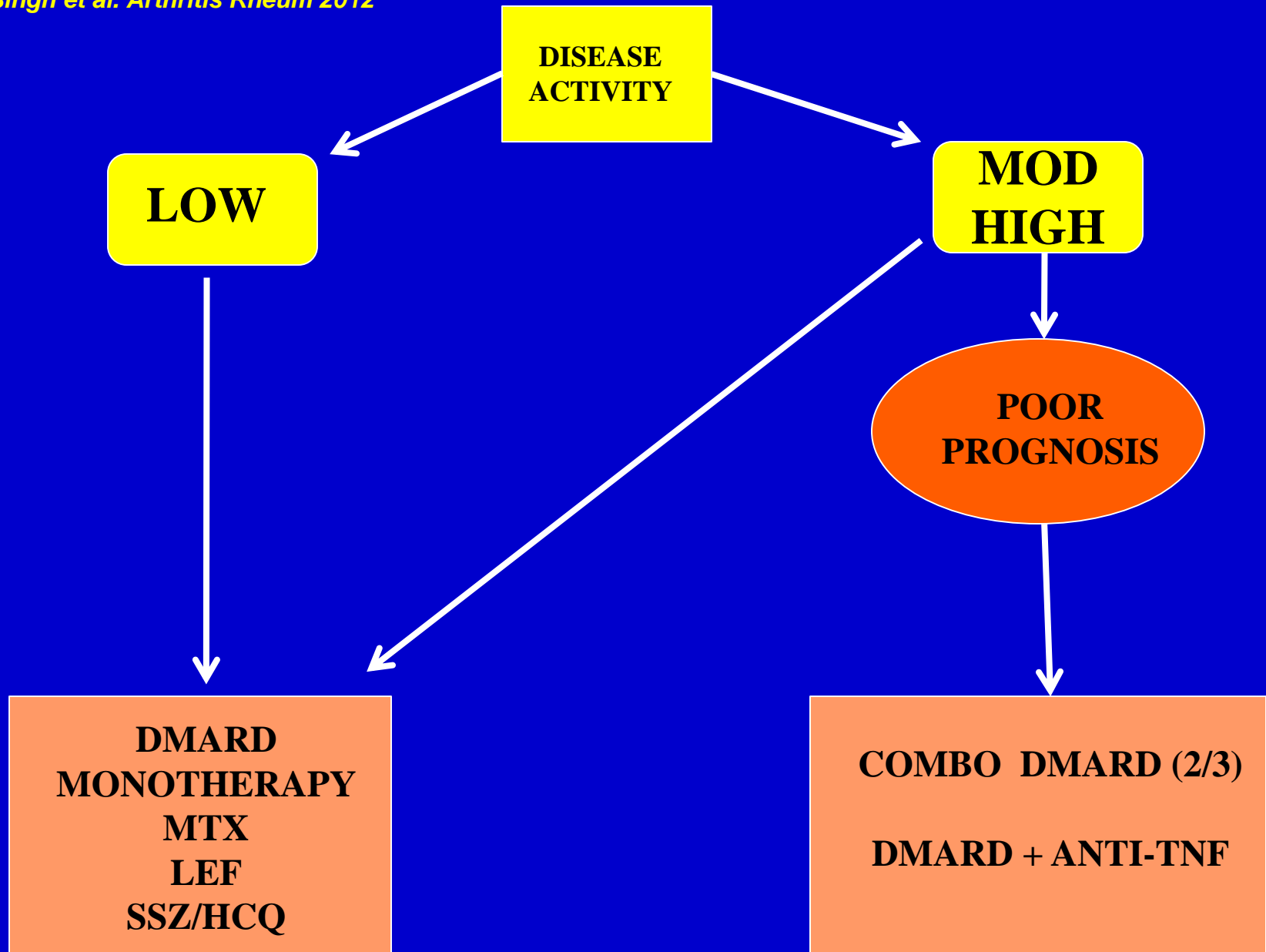
- Tofacitinib (XELJANZ, Jakvinus) – oral JAK inhibitor (JAK 3, JAK 1)

Poor Prognostic Factors in RA

- Early age at onset
- Polyarticular disease (increasing number of joints)
- Systemic extra-articular disease (nodules, vasculitis, eye disease, interstitial lung disease)
- High-titer RF positive
- Anti-CCP antibody positive
- Persistent disease activity (high ESR, CRP, disease activity scores)
- HLA-DRB1 “shared epitope” positive
(strongest known genetic risk factor for RA)

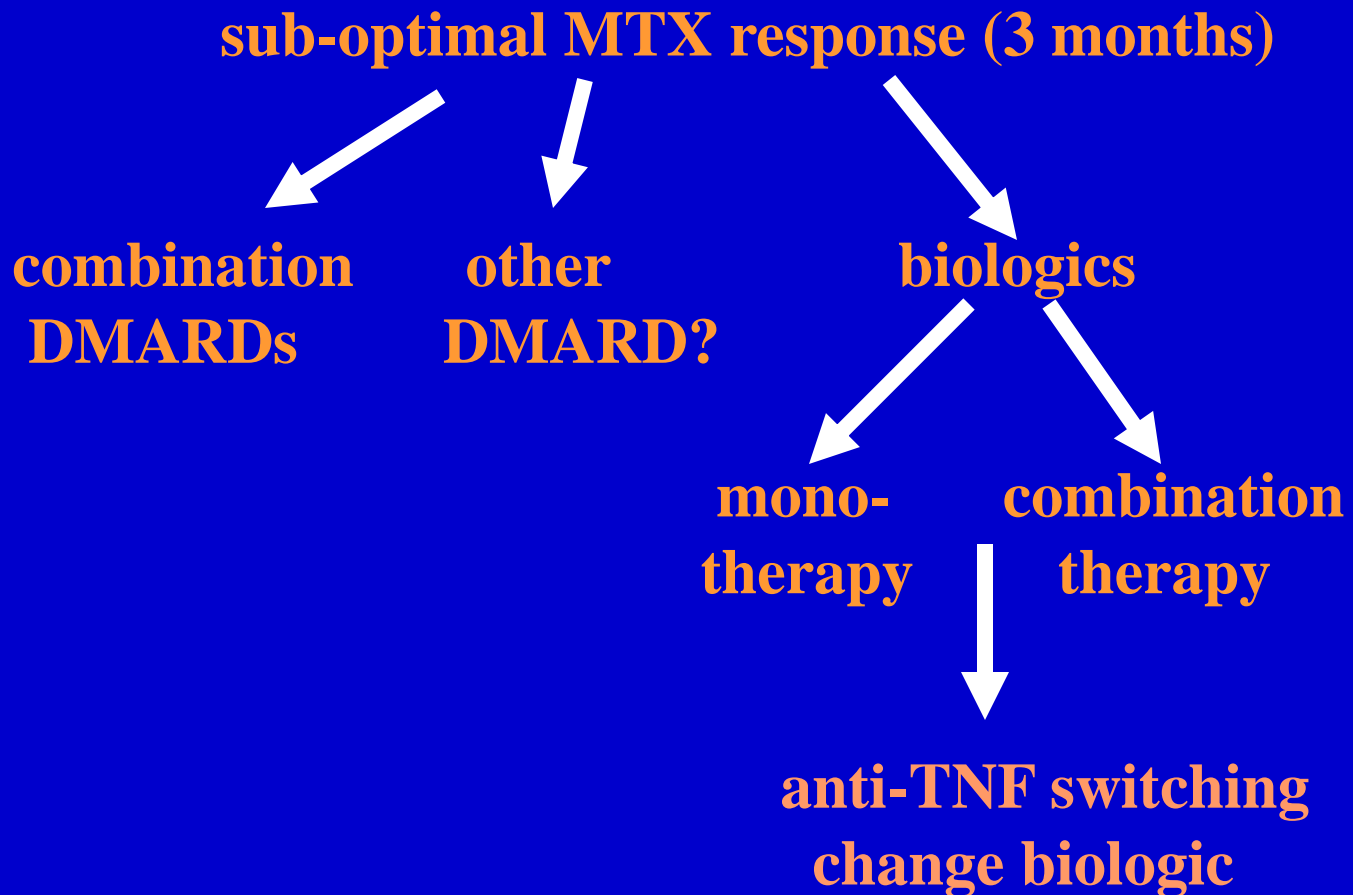
Standard Treatment in Early RA (< 6 months)

Singh et al. Arthritis Rheum 2012



Inadequate response to MTX

Smolen JS et al. Ann Rheum Dis 2013



Optimizing Treatment Response

Target low disease activity/remission

Weinblatt ME et al: *Arthritis Rheum* 2008; Dervieux T et al: *Rheumatology* 2010

O'Dell JR et al: *NEJM* 2013; Scott et al : *BMJ* 2015

O'Dell JR et al: *Arthritis Rheum* 2013; Villeneuve E, Haroui B: *Int J Adv Rheumatol* 2006

De Punder YMR et al: *Rheumatology* 2012

Saevarsdottir S et al. *Arthritis Rheum* 2011

- **Optimizing MTX response (monotherapy or combination therapy)**
 - Dose – can increase to 20-25 mg/week
 - Route – SC, IM
 - ? Role of MTX polyglutamate levels (whole blood MTX levels)
 - 30% achieve low disease activity/remission with MTX alone
- **Use combination DMARDs or MTX plus anti-TNF early (step up)**
 - another 30-40% achieve low disease activity/remission
- **Stop smoking**
- **Switch anti-TNFs or to other biologics as needed**
 - dose increase not effective with anti-TNFs
- **Monitor disease activity – clinical, ultrasound, biomarkers – CRP, Vectra (MBDA score) - TREAT TO TARGET (LDA/REM)**

What about corticosteroids?

Wassenberg S et al: Arthritis Rheum 2005; Smolen JS et al. Ann Rheum Dis 2013

- Low dose prednisone/prednisolone (<7.5mg/day) reduces inflammation and radiographic progression
- EULAR recommendation – consider at start
- High doses should not be used
- IM methylprednisolone can be used for flares, bridge therapy
- Concern regarding long term side effects - glucose intolerance, osteoporosis, infections, H Zoster, CV risk

Stopping biologics (anti-TNFs)

Why Stop?

- Remission is achievable (?20-30%) with DMARD + anti-TNF agents and low disease activity is attained in the majority – but is it lasting off drug?
- Short and long term side effects of anti-TNF agents – skin, infection, opportunistic infection, granulomatous inflammation
- Cost of anti-TNF agents
- Patient preference – these are injectables, infusions

Stopping anti-TNFs

Uncontrolled Studies

Van den Broek et al. ARD 2011: **BeSt study**. **Active early RA** (< 2years) –IFX + MTX. 104 pts $DAS \leq 2.4$ (mean 1.3) for ≥ 6 mos – IFX d/c . 50/104 (**48%**) flared in 3-6mos. **Successfully reintroduced in 84%**

Tanaka et al. A&R 2012 (abstract): **HONOR Study**: 51 pts on ADA + MTX - $DAS\ 28\text{-}ESR < 2.6 \geq 6$ mos, ADA d/c followed for 12 mos. Mean disease dur'n 7.1yrs - **27/42 (64%) flared**. **Deeper remission ($DAS < 1.9$) and shorter disease duration** correlated with remission maintenance

Stopping Anti-TNFs

Recent Controlled Trials

Smolen JS et al . Lancet 2013; Smolen JS et al . Lancet 2014; Emery P et al. NEJM 2014

PRESERVE Trial: Patients with active RA (mean disease duration app 7yrs) put on MTX + ETA (50mg/wk). Those with LDA for 3-9mos randomized (blinded) to:
MTX + placebo (ETA stopped); MTX + ETA 25mg; MTX + ETA 50mg
LDA maintained @ 36 wks? 43% vs 79% vs 83%

OPTIMA TRIAL: Patients with active RA (< 1 yr) in RCT for ADA +MTX. Those achieving LDA randomized to ADA withdrawal or not.
LDA maintained @ app 52 weeks? 54% vs 70%

PRIZE TRIAL: ETA + MTX similar to PRESERVE but early RA (< 1 yr) to 3 gps:
placebo (no MTX or ETA); MTX + placebo (no ETA); MTX + ETA 25mg
LDA/REM maintained @ 39 wks? 23% vs 40% vs 63%

Stopping anti- TNFs

Is it possible – yesFlare Rate: 30-65%

Predictors of sustained remission (clinical):

“deep remission” (DAS28<1.9), low HAQ, prolonged duration of remission, short duration RA (early RA)

Predictors of flare (imaging):

MSKUS Power Doppler (PD) (Saleem et al. Ann Rheum Dis 2012, Foltz et al. A&R 2012)

If PD present flare OR 4-6

Stopping Anti-TNF Agents in Rheumatoid Arthritis (STARA) Trial

- Double-blind
- Placebo-controlled (2:1 placebo:drug)
- Stopping trial – 48 weeks (8 week run in, 52 week FU)
- Patients taking infliximab, adalimumab or etanercept
- Taking traditional DMARD
- NIAMS/Extramural site collaboration- academic and private practice sites

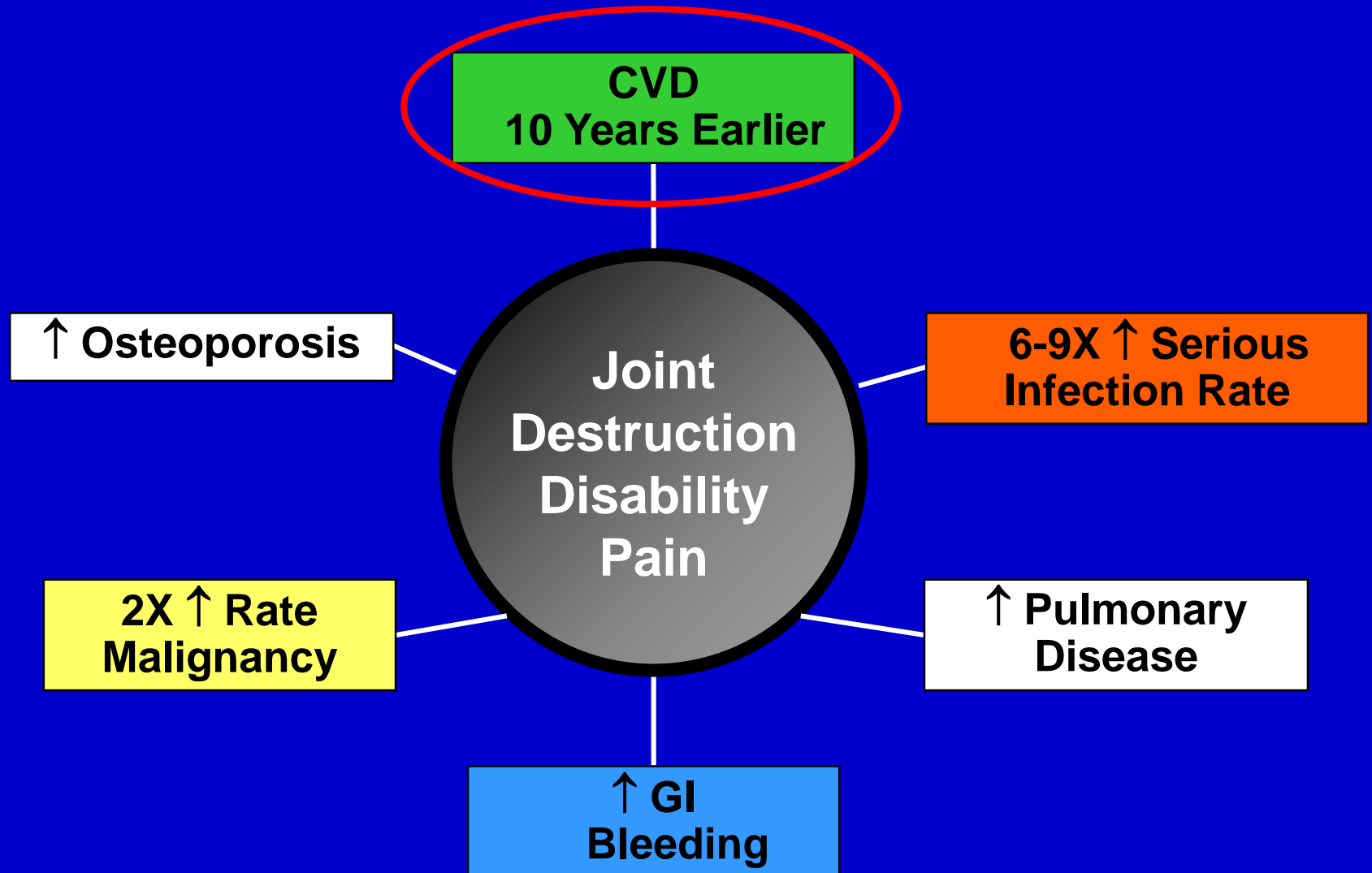
Flare Rate and Predictors of Flare

STARA Trial

1. Baseline depth of remission (DAS 28, SDAI<3.3, ACR/EULAR) and other clinical data, smoking
2. Baseline imaging (ultrasound, MRI)
3. Baseline flow cytometry, genetics (shared epitope) and gene expression profiles, cytokine profiles

“CAN A CLINICAL/ IMAGING/LABORATORY PROFILE PREDICT WHICH PATIENTS WILL FLARE AND WHICH WILL NOT?”

RA: It's Not Just the Joints!!



What has Modern RA Therapy Accomplished? A GREAT DEAL

- **Chronic deforming/ destructive RA greatly reduced and delayed**
- **Quality of life greatly improved**
- **Secondary amyloidosis almost gone**
- **Rheumatoid vasculitis (high mortality) now very rare**

- **CV fatality rate has decreased – RA with LDA**

GRACIAS