Evidence-based Progress in the Management of Rheumatoid Arthritis

Cheng Yew Kuang
Rheumatologist
Singapore

24 July 2016

MCQ 1

A 38 year-old Chinese lady, Ms RA, presented with inflammatory pain affecting both wrist for the past 6 weeks associated with early morning stiffness and swelling. Clinical examination reviewed bilateral bogginess of the wrist and metacarpal phalangeal joints. Her ESR and CRP was normal. Her RF and anti-CCP was positive. Which one of the following is the appropriate course of action?

a) To start on systemic steroids and to monitor for 3 months before starting a DMARDs (Disease Modifying Anti-Rheumatic Drugs) only if ESR and CRP are elevated
b) To start on NSAID and to monitor for 3 months before starting steroids only if ESR and CRP are elevated
c) To start DMARDs
d) To order an MRI wrists and start DMARDs if there are synovitis
e) To order an X ray of both wrist and start DMARDs if there are erosions

Lesson #1

Early diagnosis and early treatment is the key to good outcome in

Rheumatoid Arthritis

Disease overview: rheumatoid arthritis

- Rheumatoid arthritis (RA) is a chronic, progressive and destructive autoimmune disease[1]
- As the disease progresses, irreversible joint damage lead to loss of function and physical disability[2]

Lifelong condition

Characterised by painful inflammation of the joint lining

Suffer from pain, swelling, loss of movement

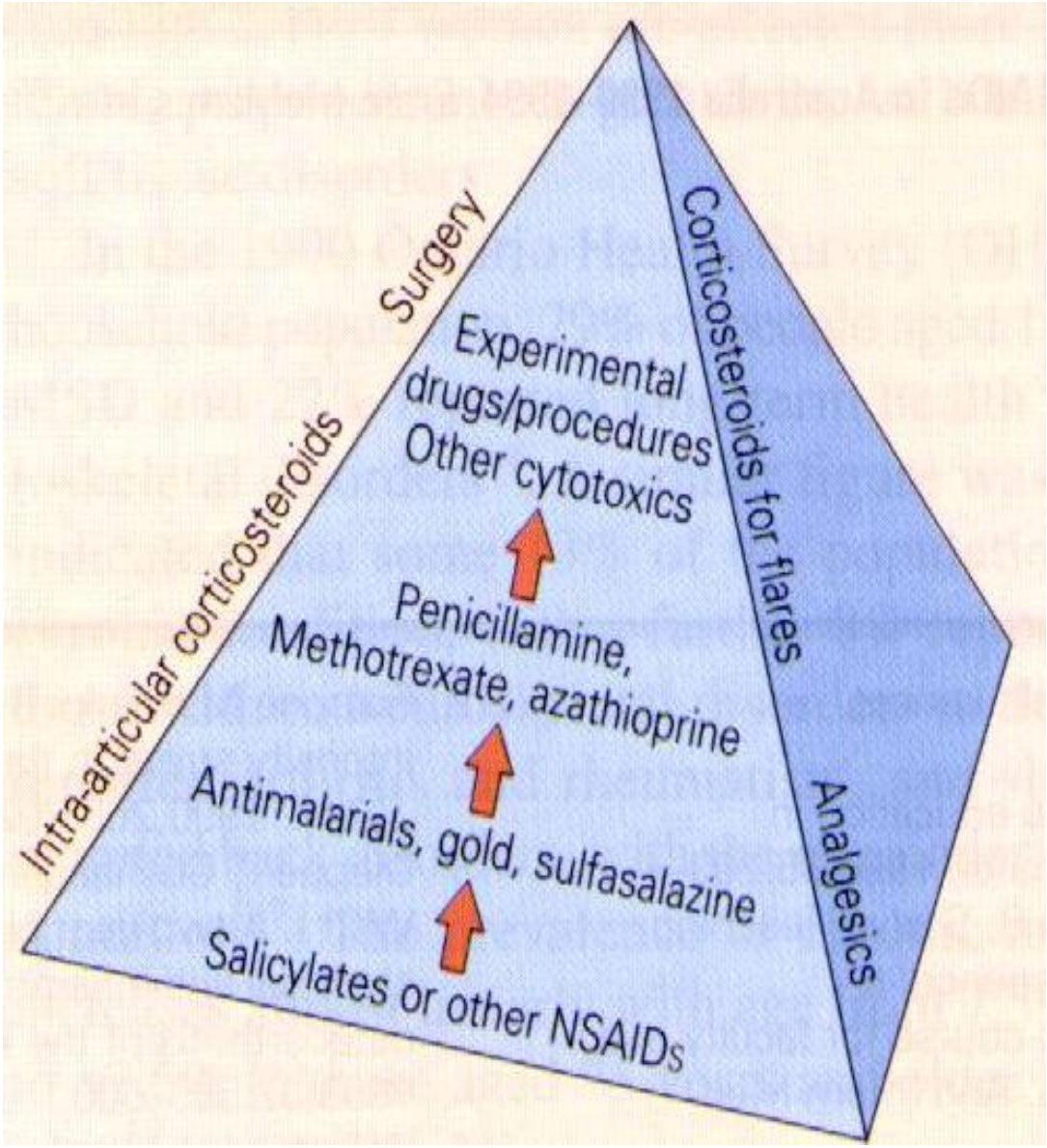
Eventually complete destruction of the joint

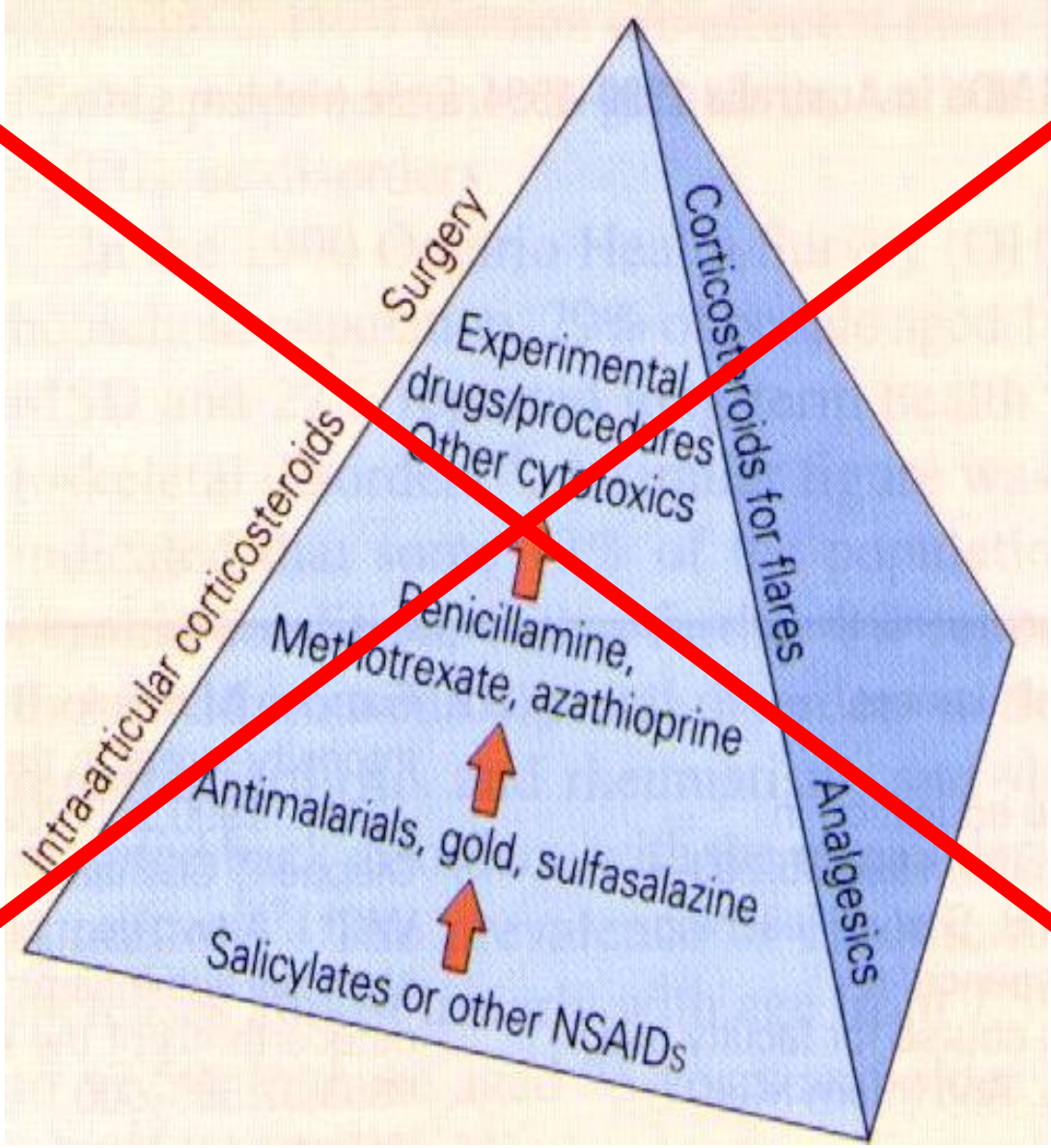
Greater risk for comorbid conditions including:

- **Cardiovascular disease:**
  - **congestive heart failure**
  - **coronary heart disease**
  - **stroke**
- **Respiratory disease**
- **Depression and/or anxiety**

- Associated with a reduction in life expectancy of 5 to 10 years[3]

1. Firestein GS. In: Kelley's Textbook of Rheumatology. 7th ed. Philadelphia, PA: Elsevier Saunders; 2005;2:996-1000;
2. Genovese MC, Harris ED Jr. In: Kelley's Textbook of Rheumatology. 7th ed. Philadelphia, PA: Elsevier Saunders; 2005;2:1029-1101; 3. Kvien TK. Pharmacoeconomics 2004;22(2 Suppl 1):1-12.


Surgery
Corticosteroids for flares
Intra-articular corticosteroids
Experimental drugs/procedures
Other cytotoxics
Penicillamine, Methotrexate, azathioprine
Antimalarials, gold, sulfasalazine
Salicylates or other NSAIDs
Analgesics


Surgery
Corticosteroids for flares
Intra-articular corticosteroids
Experimental drugs/procedures
Other cytotoxics
Penicillamine,
Methotrexate, azathioprine
Antimalarials, gold, sulfasalazine
Salicylates or other NSAIDs
Analgesics

Conventional Synthetic DMARD (csDMARD)

- Methotrexate
- Sulphasalazine
- Plaquenil
- leflunomide - LEF
- D Penicillamine
- Azathioprine
- Cyclosporine
- Gold

Biological DMARD (bDMARD)

- anti-TNFα mAb (e.g. Enbrel, Humira, Remicade)
- rIL-1 Ra (e.g. Anakiret)
- Anti-IL6 (e.g. Tociluzumab)
- B cell depletion therapy (e.g. Rituximab)
- Co-stimulation blockage (e.g. Abatacept)

Introduction

Biologics definition

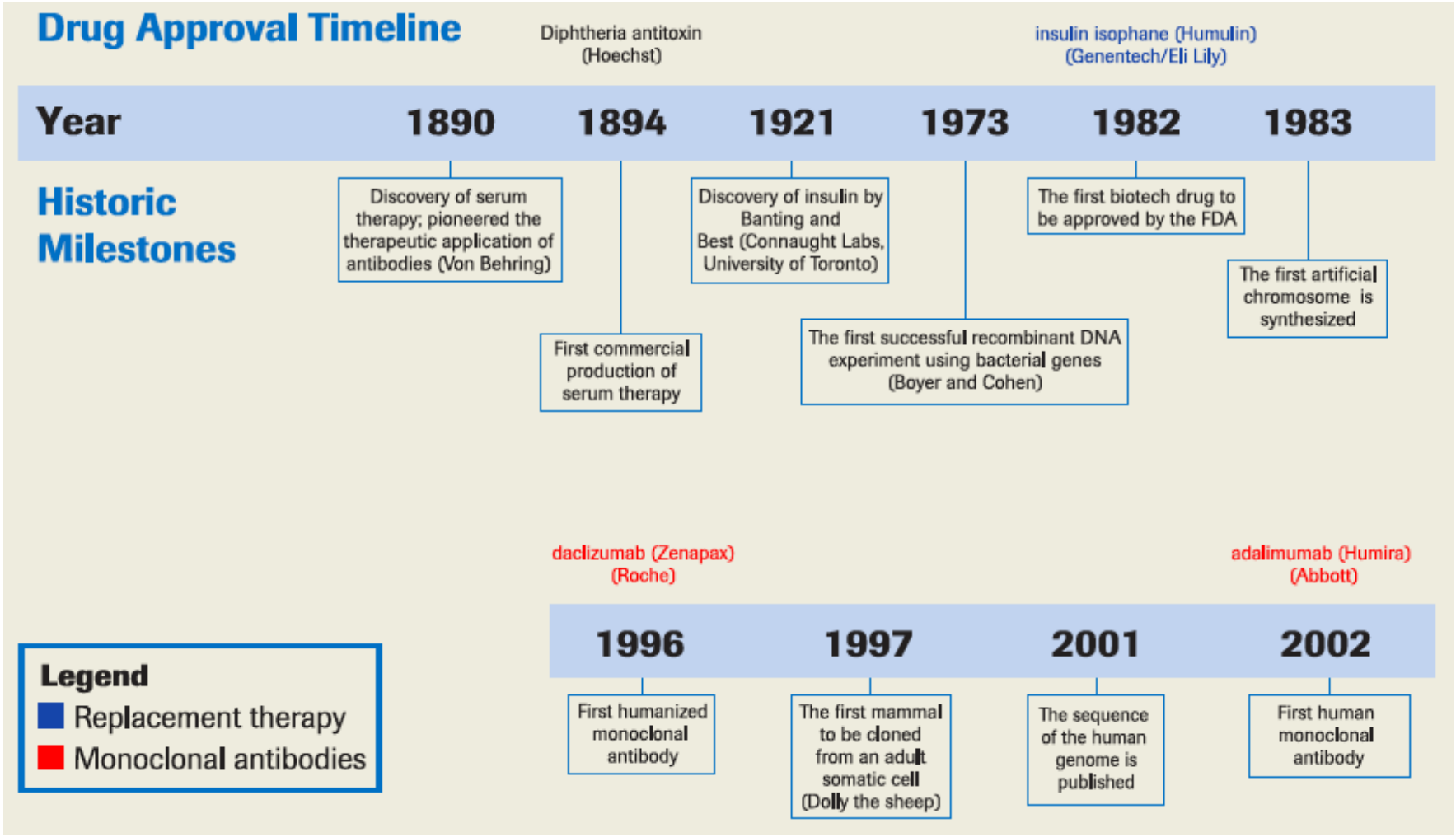
Biologics

... defined as a medicinal product produced from or extracted from a biological (living) system. Biologics can be made up of living cells or tissues or complex protein structures and can be sourced from microorganisms (such as bacteria) and animal or human tissue.

... refers to medicines produced using recombinant DNA technology

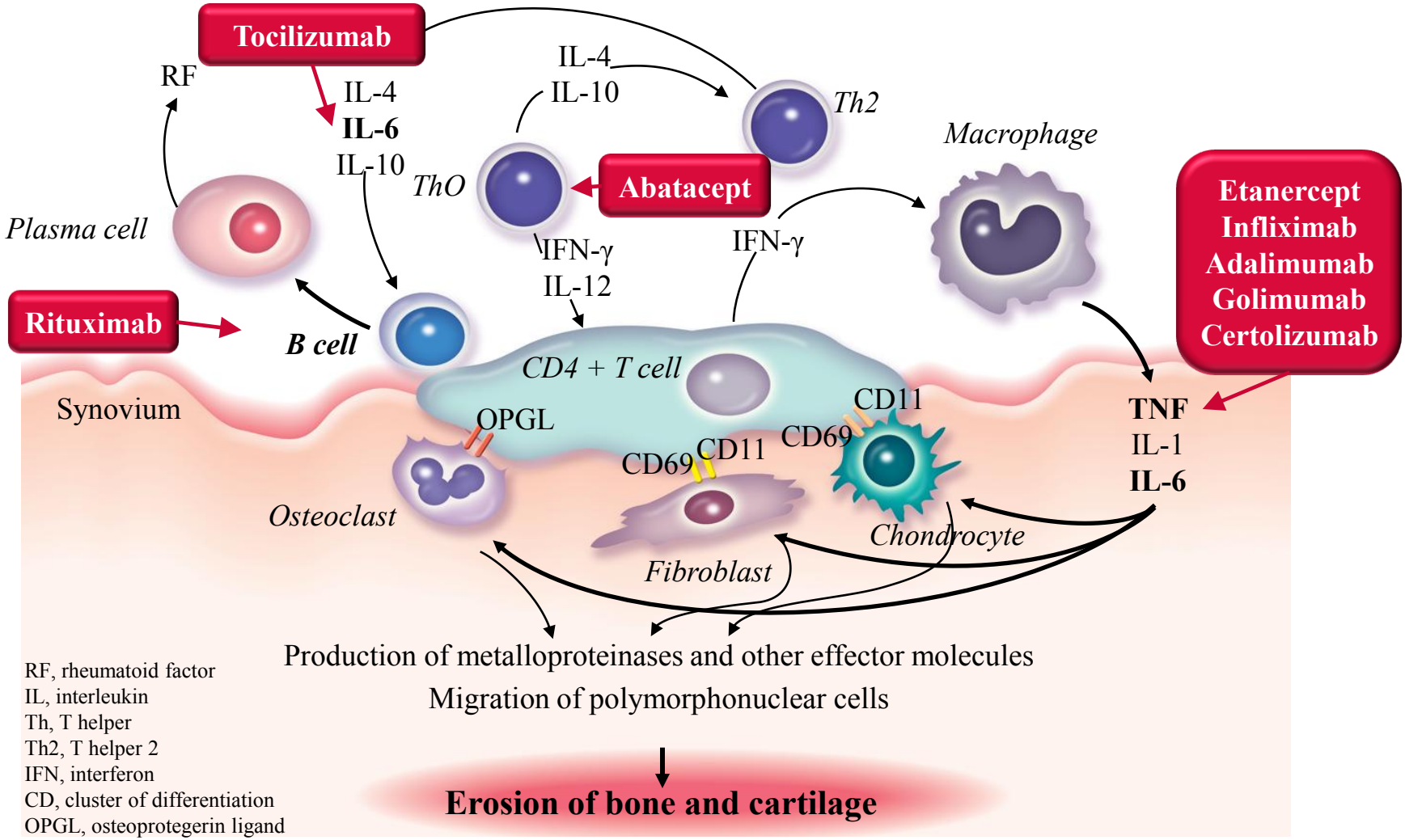
Introduction

Timeline of development of biologics



(Adapted from Revers et al. 2010)

Current biologic therapies target specific cytokines



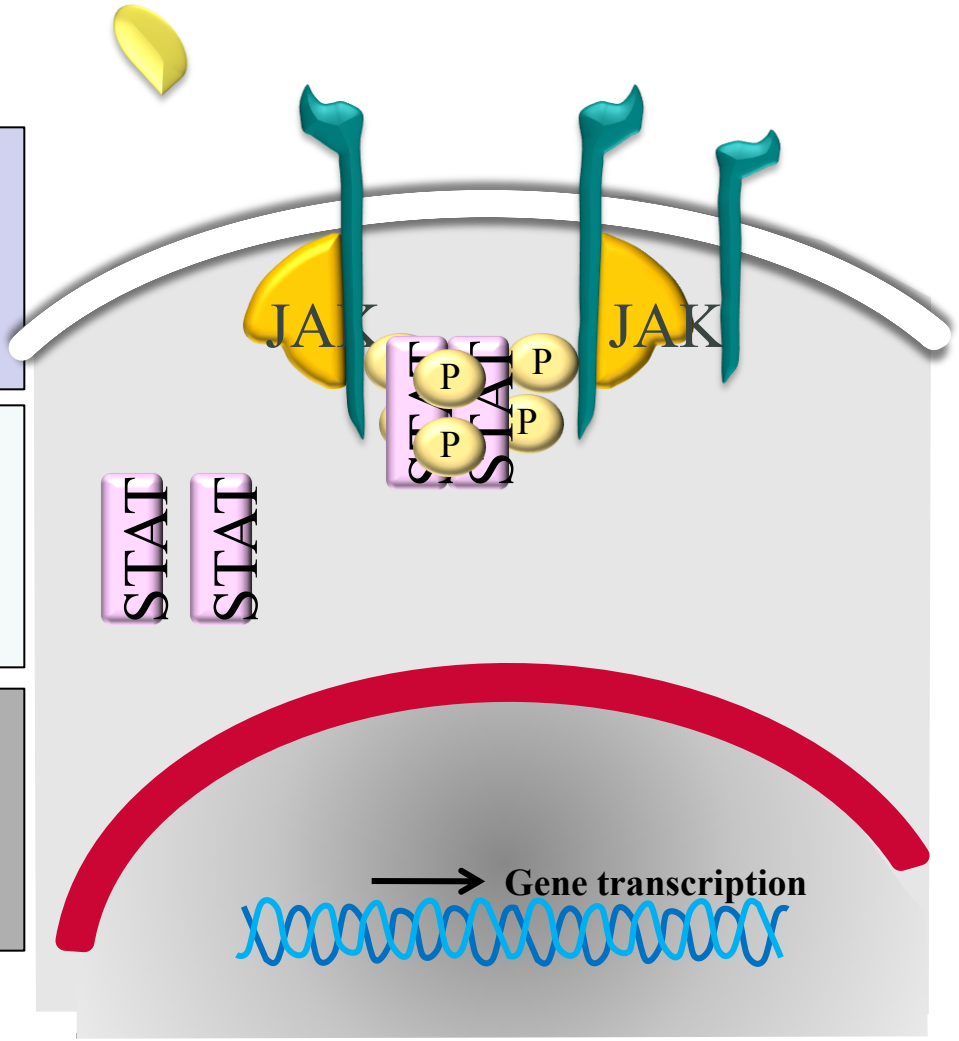
RF, rheumatoid factor
IL, interleukin
Th, T helper
Th2, T helper 2
IFN, interferon
CD, cluster of differentiation
OPGL, osteoprotegerin ligand

Cytokine binding of cytokine receptors activates JAK pathway signaling

1 Cytokines bind to cell surface receptors, which leads to receptor polymerization and activation of associated JAKs

2 Activated JAKs phosphorylate the receptors that dock STATs

3 Activated JAKs phosphorylate STATs, which dimerize and move to the nucleus to activate new gene transcription



JAK, Janus kinase; P, phosphate; STAT, signal transducer and activator of transcription

Figure adapted from Shuai K, Liu B. *Nat Rev Immunol* 2003;3:900-911.

XELJANZ is a JAK inhibitor -targeted synthetic DMARD (tsDMARD)

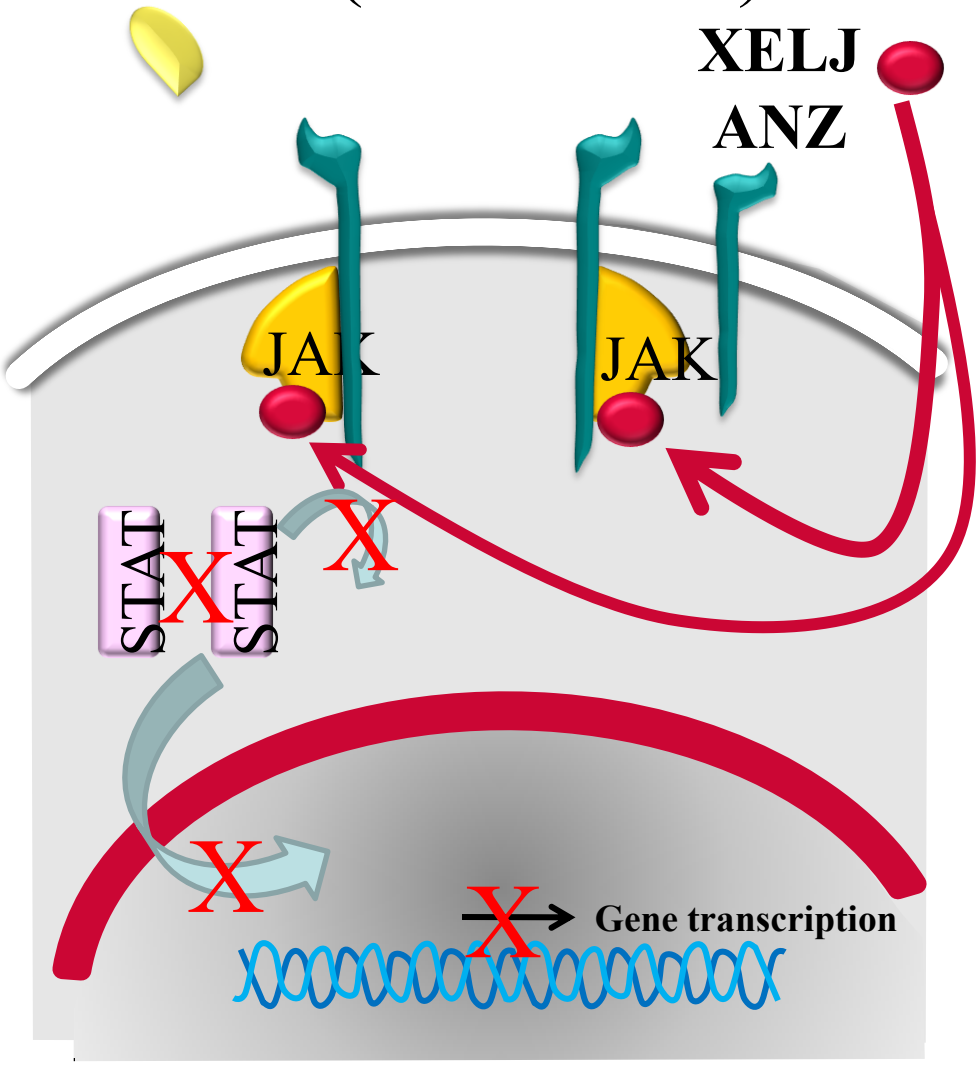
1 Cytokine binding to its cell surface receptor leads to receptor polymerization[1]

2 **XELJANZ inhibits the autophosphorylation and activation of JAK[2]**

3 JAKs cannot phosphorylate the receptors. Therefore cannot dock STATs

4 Because the STATs cannot dock, they are not phosphorylated or activated. Gene transcription and cytokine production are thereby inhibited[2]

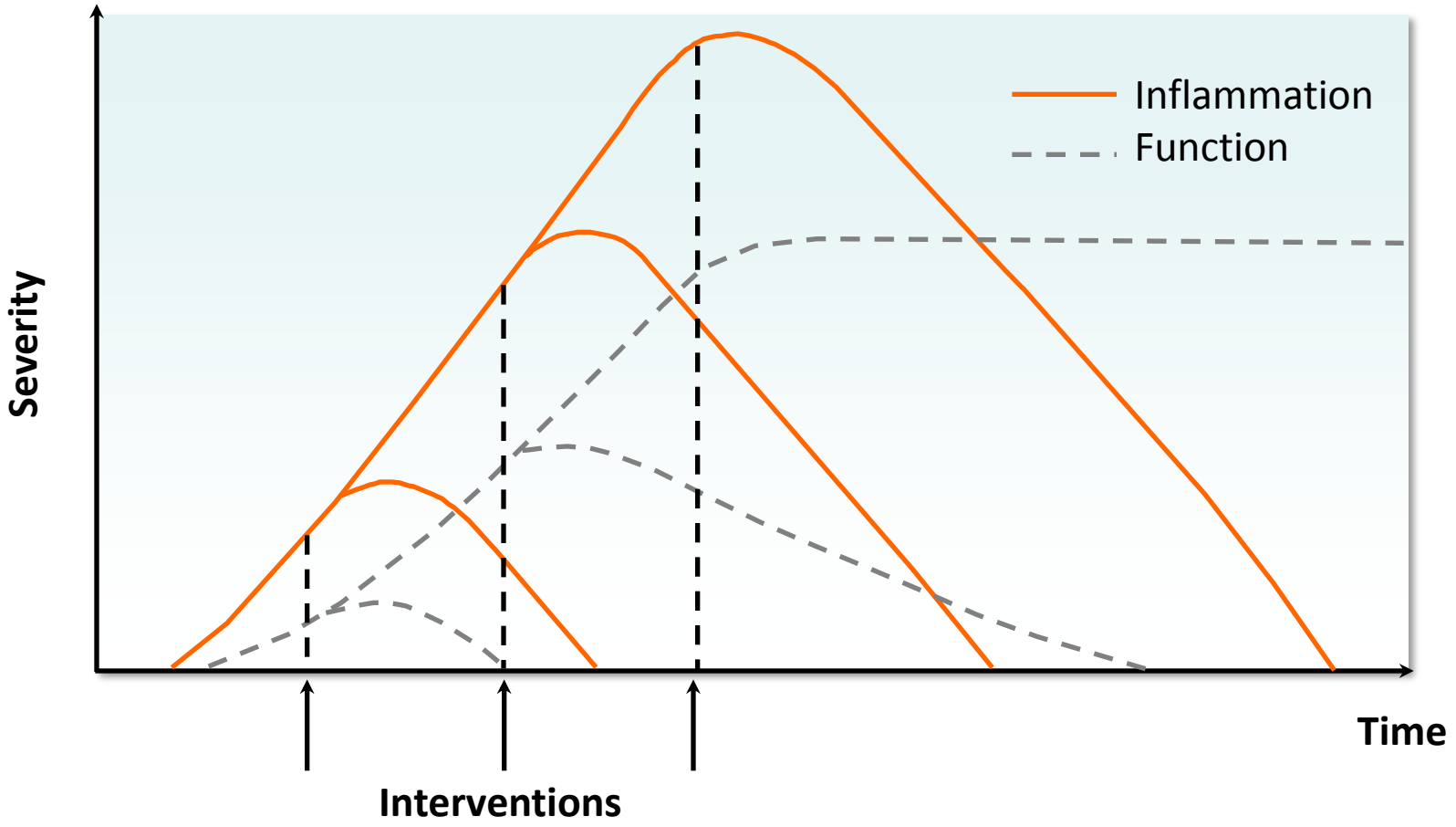
JAK, Janus kinase; STAT, signal transducer and activator of transcription



Adapted from reference 1.

1. Shuai K, Liu B. *Nat Rev Immunol* 2003;3:900-911; 2. Jiang JK, et al. *J Med Chem* 2008;51:8012-8018.

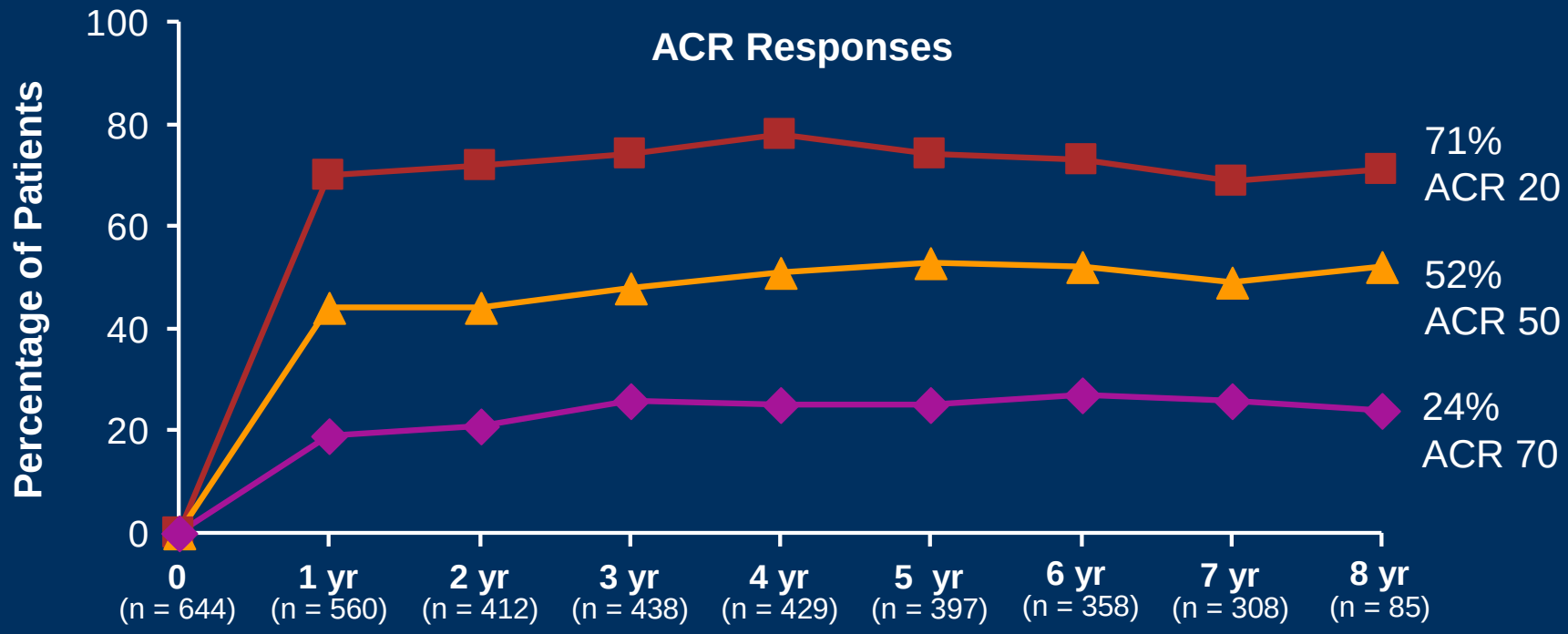
Need for early and effective treatment in RA



Adapted from Emery P, Salmon M. Ann Rheum Dis 1995; 54: 944.

Long-Term Efficacy of Etanercept in RA: Clinical Trial Database- 8 Years Experience

Mean duration of RA = 12.4 years



Long-term efficacy was evaluated in a subset of adult patients who received etanercept in initial studies and/or etanercept 25 mg BIW in the extension and had sufficient disease activity data available (n = 644).

As this extension is ongoing, this is an interim analysis whereby data are represented as “observed cases” at each time point. Results at successive time points are based on declining numbers of subjects reflecting withdrawals from the study OR subjects who had not achieved the particular time point at the time of this analysis.

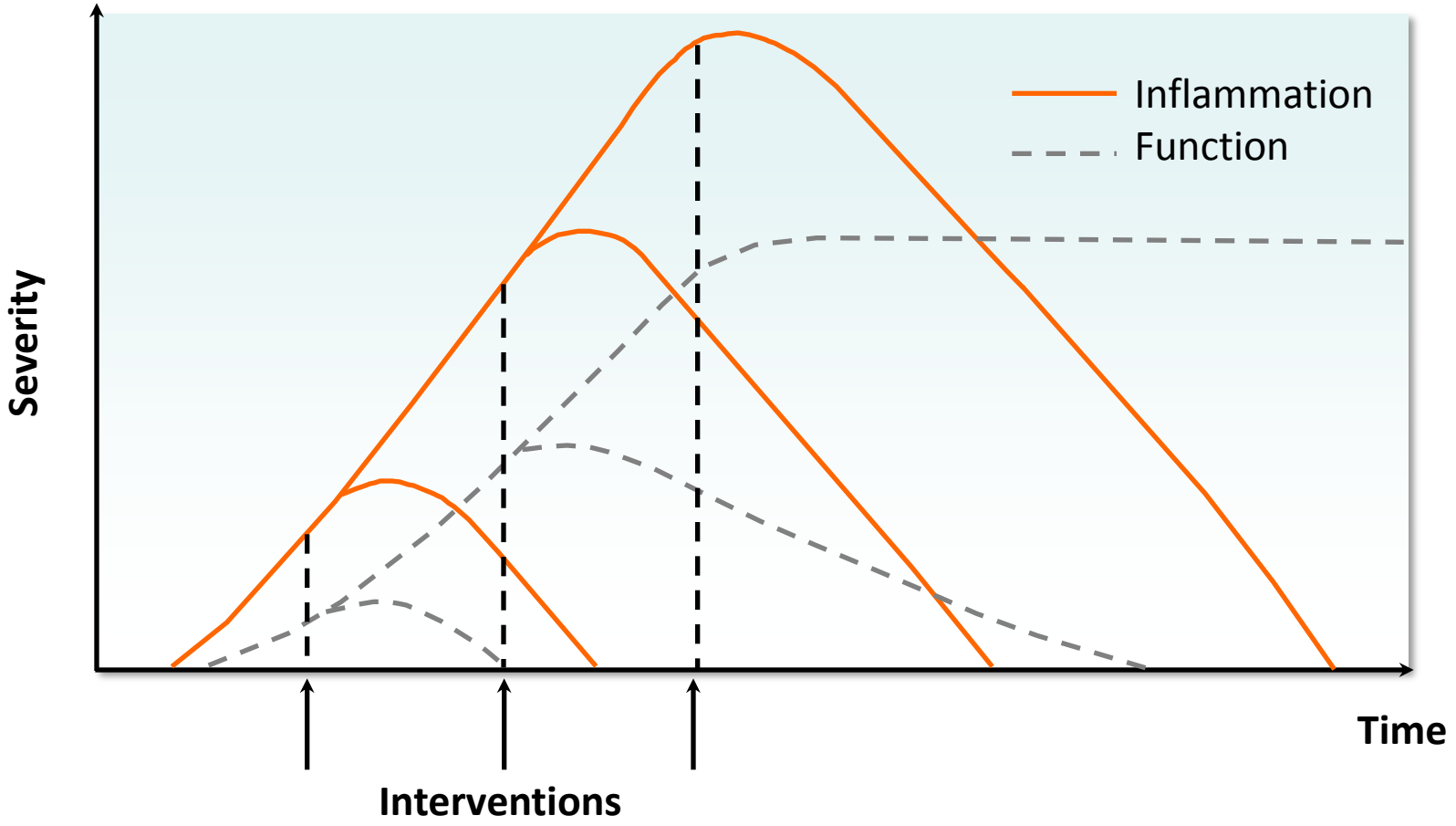
Data on file, Amgen.

American College of Rheumatology (ACR) 20/50/70 Response

- 20/50/70% reduction in
  - Tender joint count
  - Swollen joint count
- 20/50/70% improvement in three of the following
  - Patient assessment of pain
  - Physician global assessment
  - Patient global assessment
  - Patient assessment of disability
  - ESR or CRP

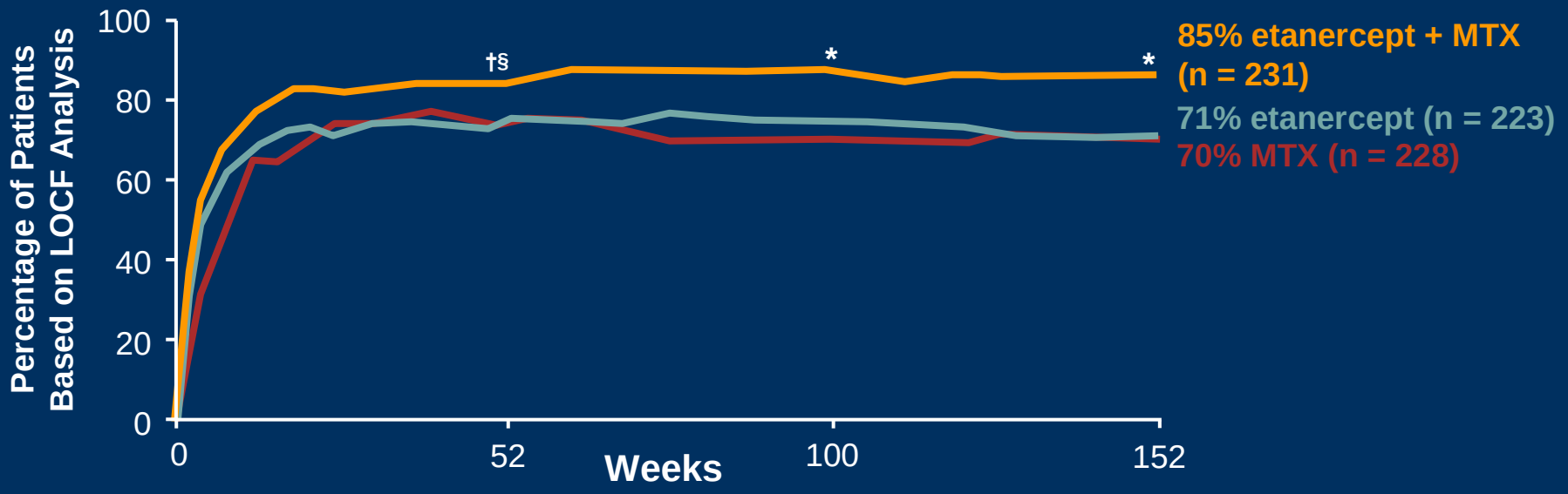
ACR 2002 Guidelines. *Arthritis Rheum*. 2002;46:328-346.

Need for early and effective treatment in RA



Adapted from Emery P, Salmon M. Ann Rheum Dis 1995; 54: 944.

ACR 20 Response Rates at 3 Years



ACR 20 Nonresponder Imputation (NRI)	1-Year NRI (%)	2-Year NRI (%)	3-Year NRI (%)[#]
MTX + etanercept	75[†‡] (n = 231)	66[†§] (n = 231)	57[†§] (n = 212)
Etanercept	66 (n = 223)	57[§] (n = 223)	44[‡] (n = 210)
MTX	59 (n = 228)	44 (n = 228)	34 (n = 219)

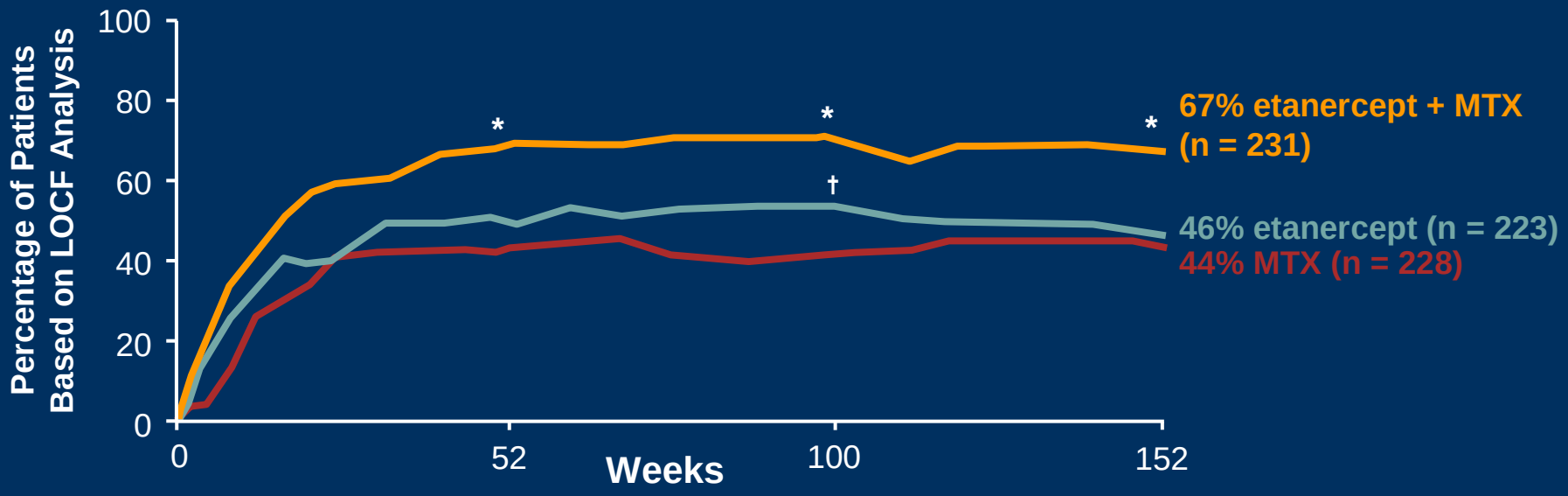
*$P < 0.01$ vs MTX and etanercept monotherapy; †$P < 0.05$ vs etanercept; ‡$P < 0.05$ vs MTX; §$P < 0.01$ vs MTX

[#]At 3 years, the ITT population differs between LOCF and NRI analyses due to the exclusion of patients enrolled at sites that were closed prior to year 3. Patients remaining in the study at the time of site closure were excluded from the NRI analysis.

Data on file, Wyeth Pharmaceuticals Inc.

Enbrel® (etanercept) Prescribing Information, Immunex Corporation, Thousand Oaks, Calif.

ACR 50 Response Rates at 3 Years



ACR 50 NRI	1-Year NRI (%)	2-Year NRI (%)	3-Year NRI (%)[#]
MTX + etanercept	63[‡] (n = 231)	57* (n = 231)	47* (n = 212)
Etanercept	43 (n = 223)	44[†] (n = 223)	32 (n = 210)
MTX	36 (n = 228)	30 (n = 228)	25 (n = 219)

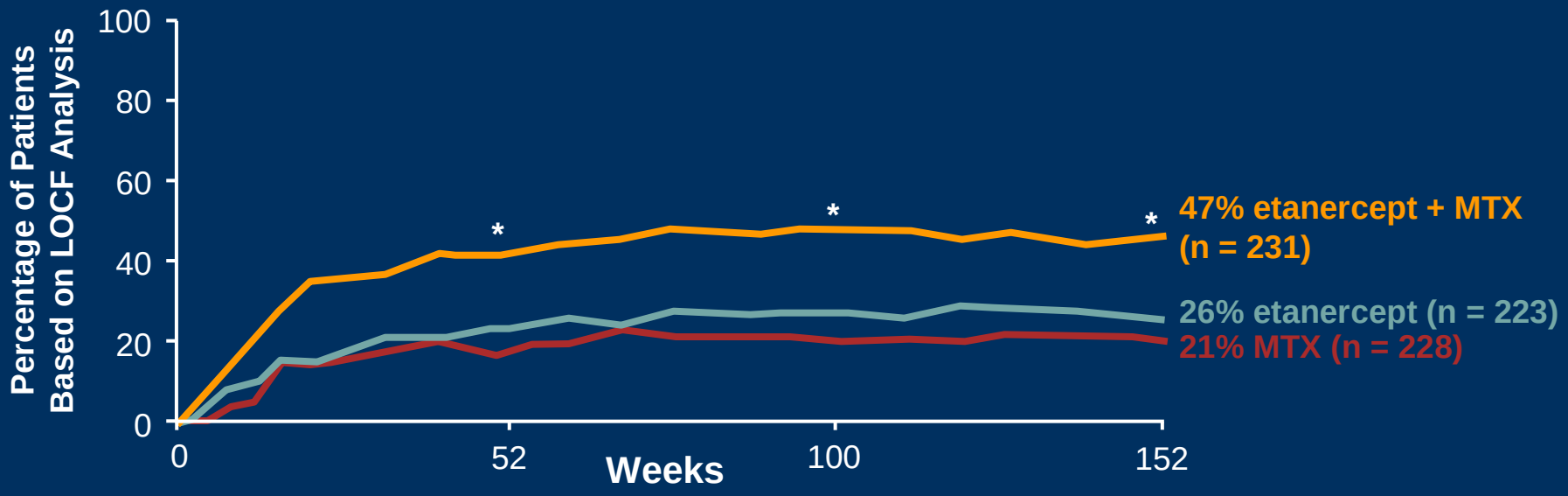
*$P < 0.01$ vs MTX and etanercept monotherapy; [†]$P < 0.01$ vs MTX; [‡]$P < 0.05$ vs MTX and etanercept monotherapy

[#]At 3 years, the ITT population differs between LOCF and NRI analyses due to the exclusion of patients enrolled at sites that were closed prior to year 3. Patients remaining in the study at the time of site closure were excluded from the NRI analysis.

Data on file, Wyeth Pharmaceuticals Inc.

Enbrel® (etanercept) Prescribing Information, Immunex Corporation, Thousand Oaks, Calif.

ACR 70 Response Rates at 3 Years



ACR 70 NRI	1-Year NRI (%)	2-Year NRI (%)	3-Year NRI (%)[#]
MTX + etanercept	40†‡ (n = 231)	41* (n = 231)	34* (n = 212)
Etanercept	22 (n = 223)	24† (n = 223)	20 (n = 210)
MTX	17 (n = 228)	16 (n = 228)	13 (n = 219)

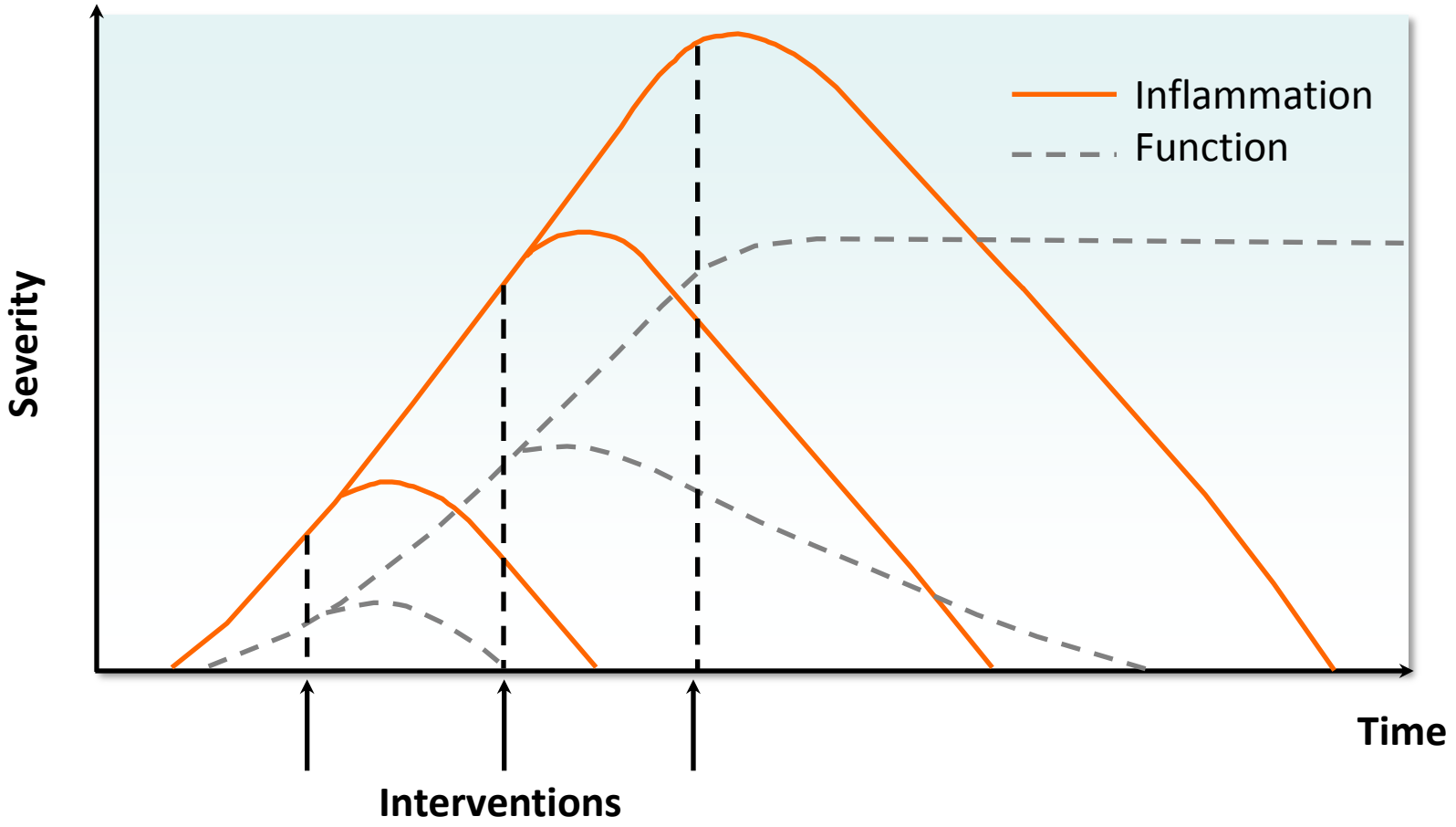
*$P < 0.01$ vs MTX and etanercept monotherapy; †$P < 0.05$ vs MTX; ‡$P < 0.05$ vs etanercept

[#]At 3 years, the ITT population differs between LOCF and NRI analyses due to the exclusion of patients enrolled at sites that were closed prior to year 3. Patients remaining in the study at the time of site closure were excluded from the NRI analysis.

Data on file, Wyeth Pharmaceuticals Inc.

Enbrel® (etanercept) Prescribing Information, Immunex Corporation, Thousand Oaks, Calif.

Need for early and effective treatment in RA



Adapted from Emery P, Salmon M. Ann Rheum Dis 1995; 54: 944.

Remission Rates in Subjects With Active Early Rheumatoid Arthritis – 1 Year Results of COMET: Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis

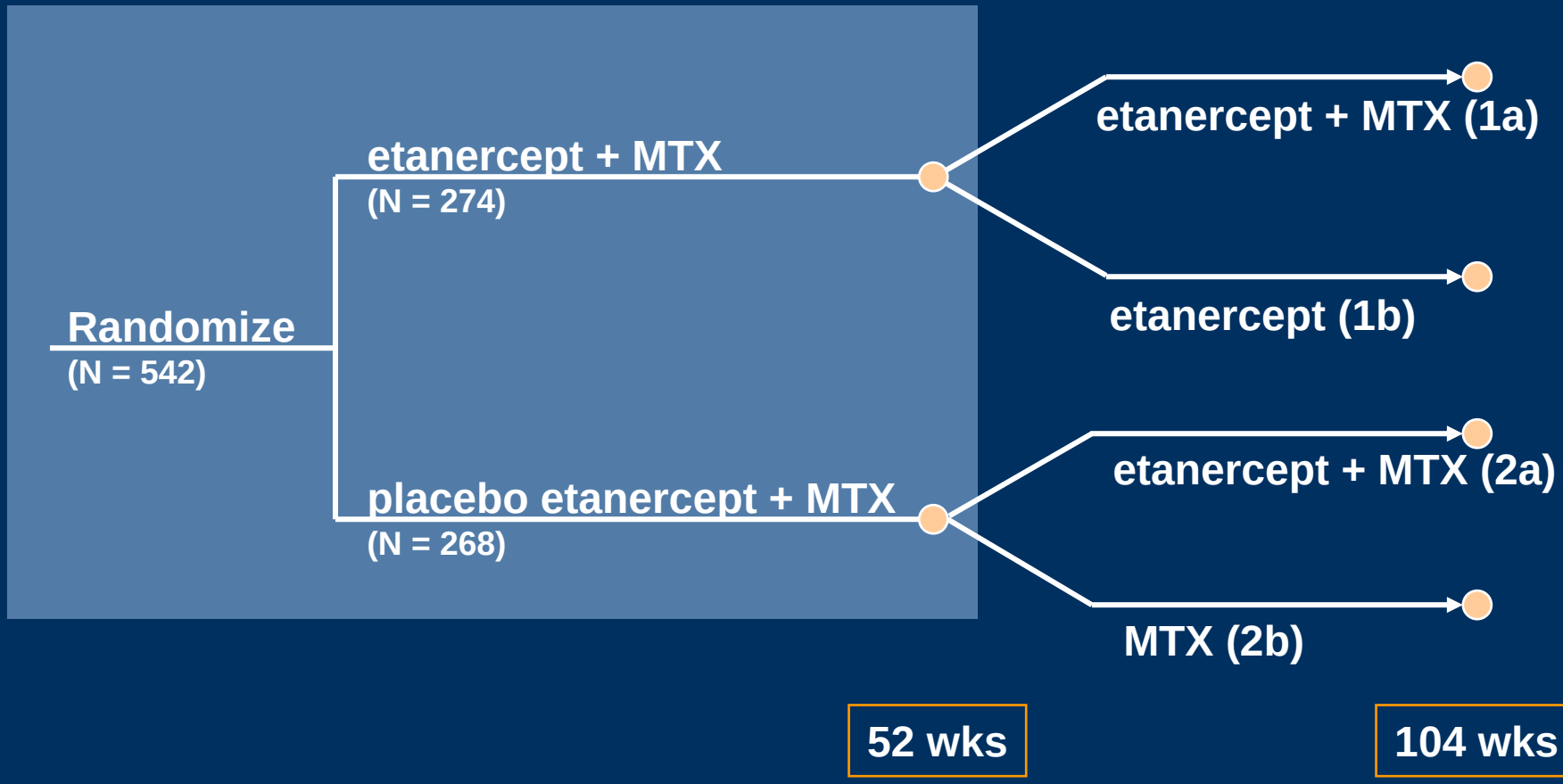
P Emery,[1] F Breedveld,[2] S Hall,[3] P Durez,[4]
R Pedersen,[5] D Robertson,[5] B Freundlich[5]

[1] University of Leeds, Leeds, UK
[2] Leiden University Medical Center, Leiden, Netherlands
[3] Cabrini Health Hospital, Malvern, Victoria, Australia
[4] Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium
[5] Wyeth Research, Collegeville, PA, USA

The Lancet Early Online Publication, 16 July 2008

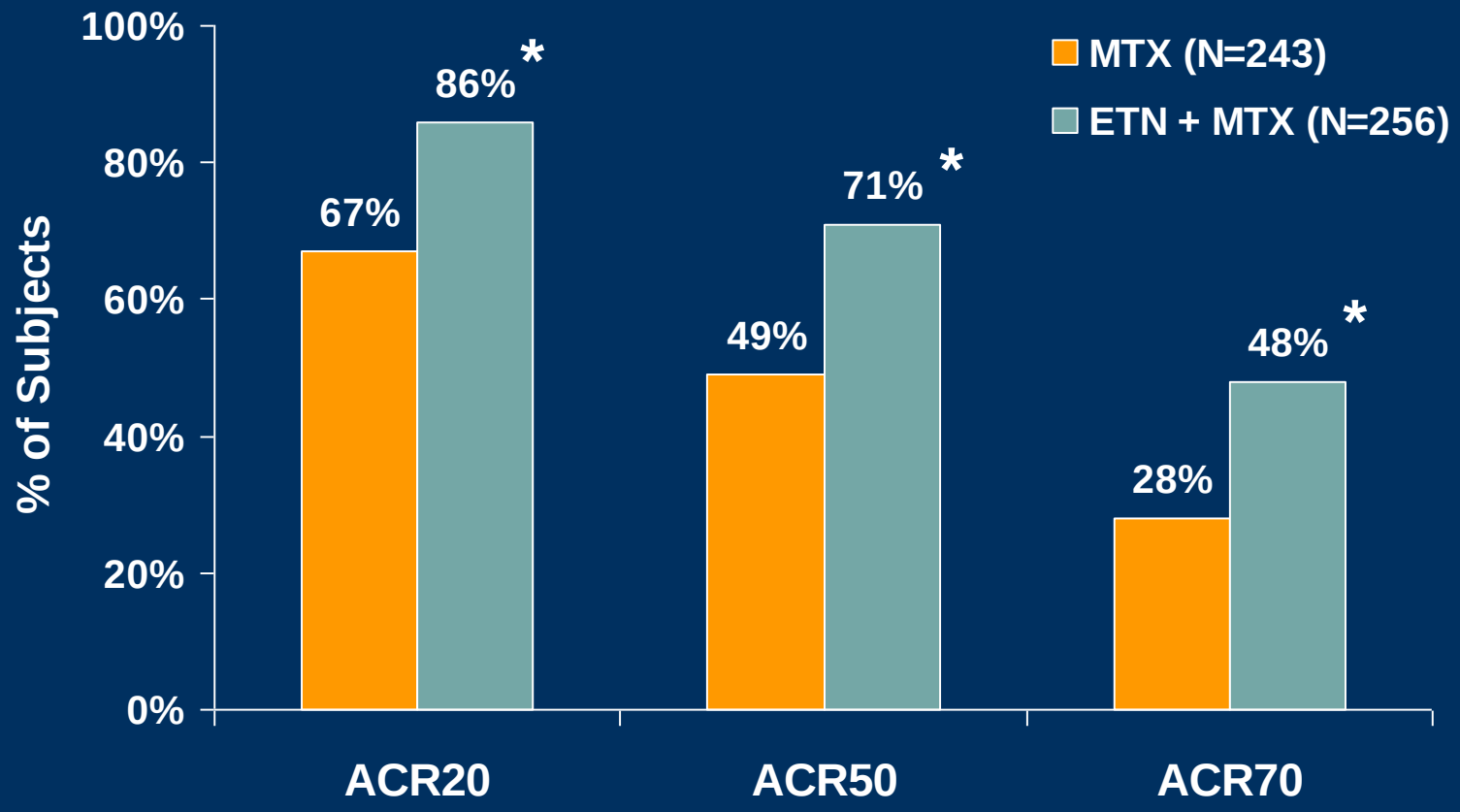
Study Design

Double-Blind Randomized Clinical Trial



Menu

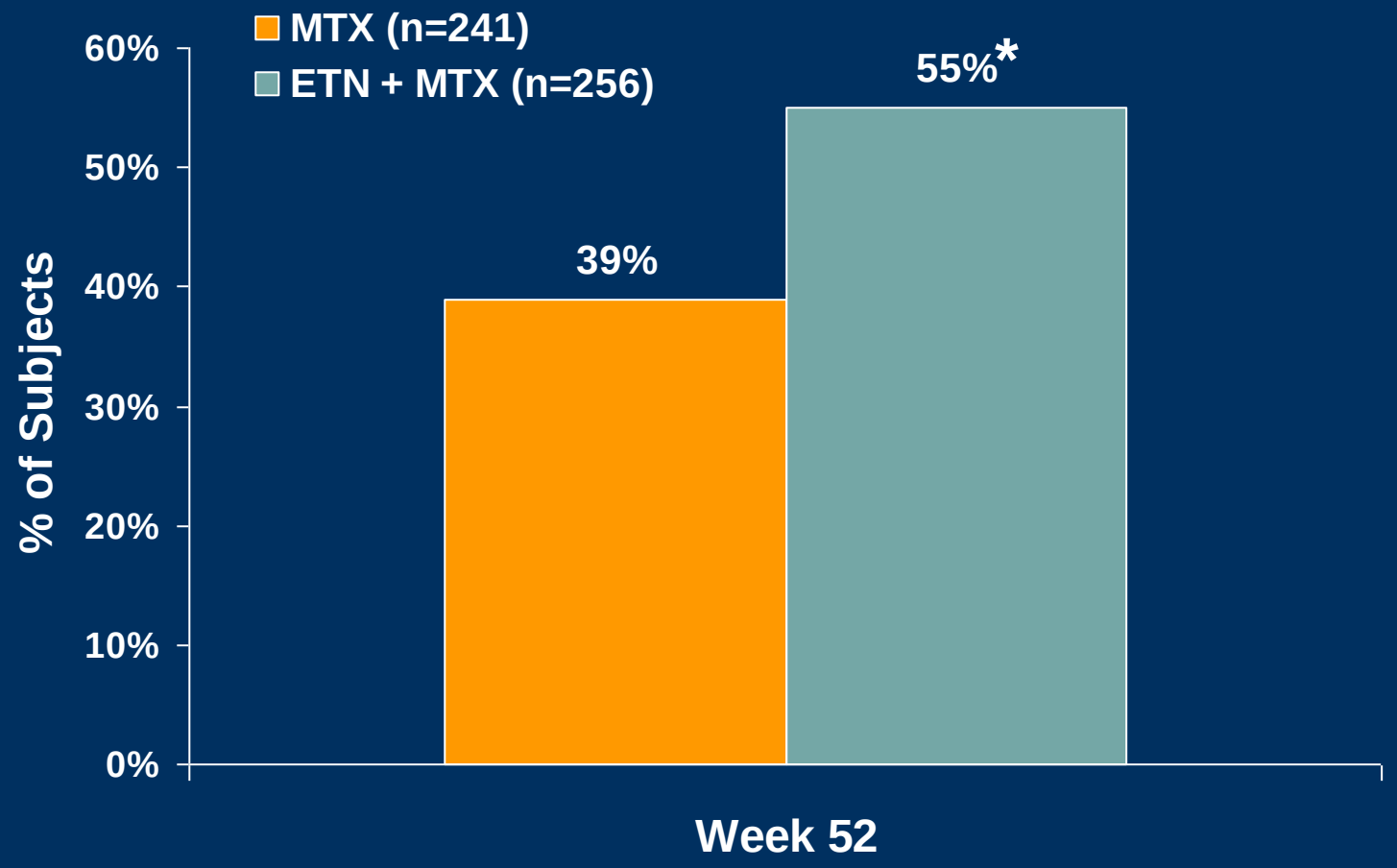
ACR Responders at Week 52



*$P < 0.001$

Menu

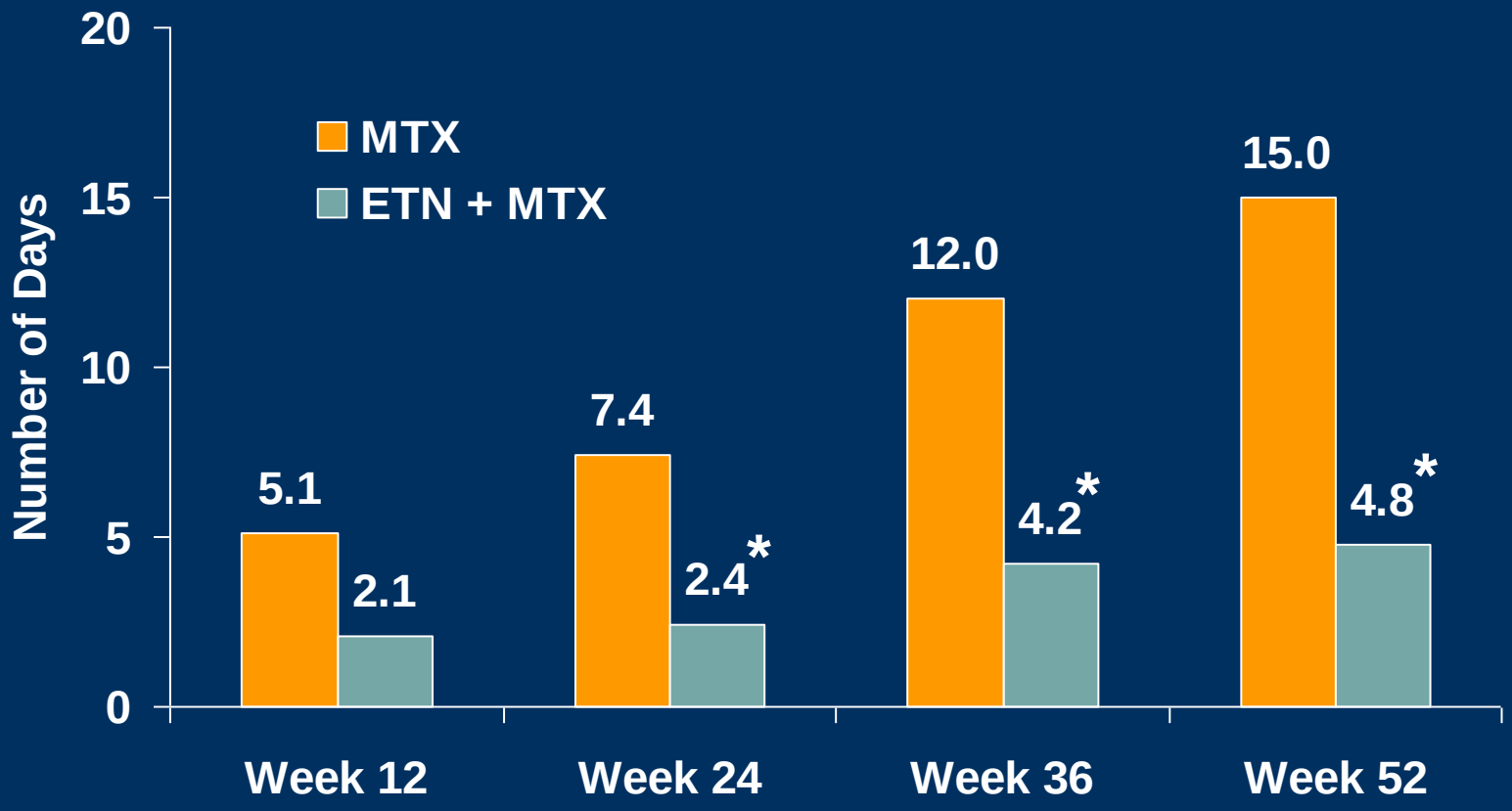
Proportion of Subjects Achieving Normal Disability Levels (HAQ ≤ 0.5) at Week 52



*$P < 0.001$

Menu

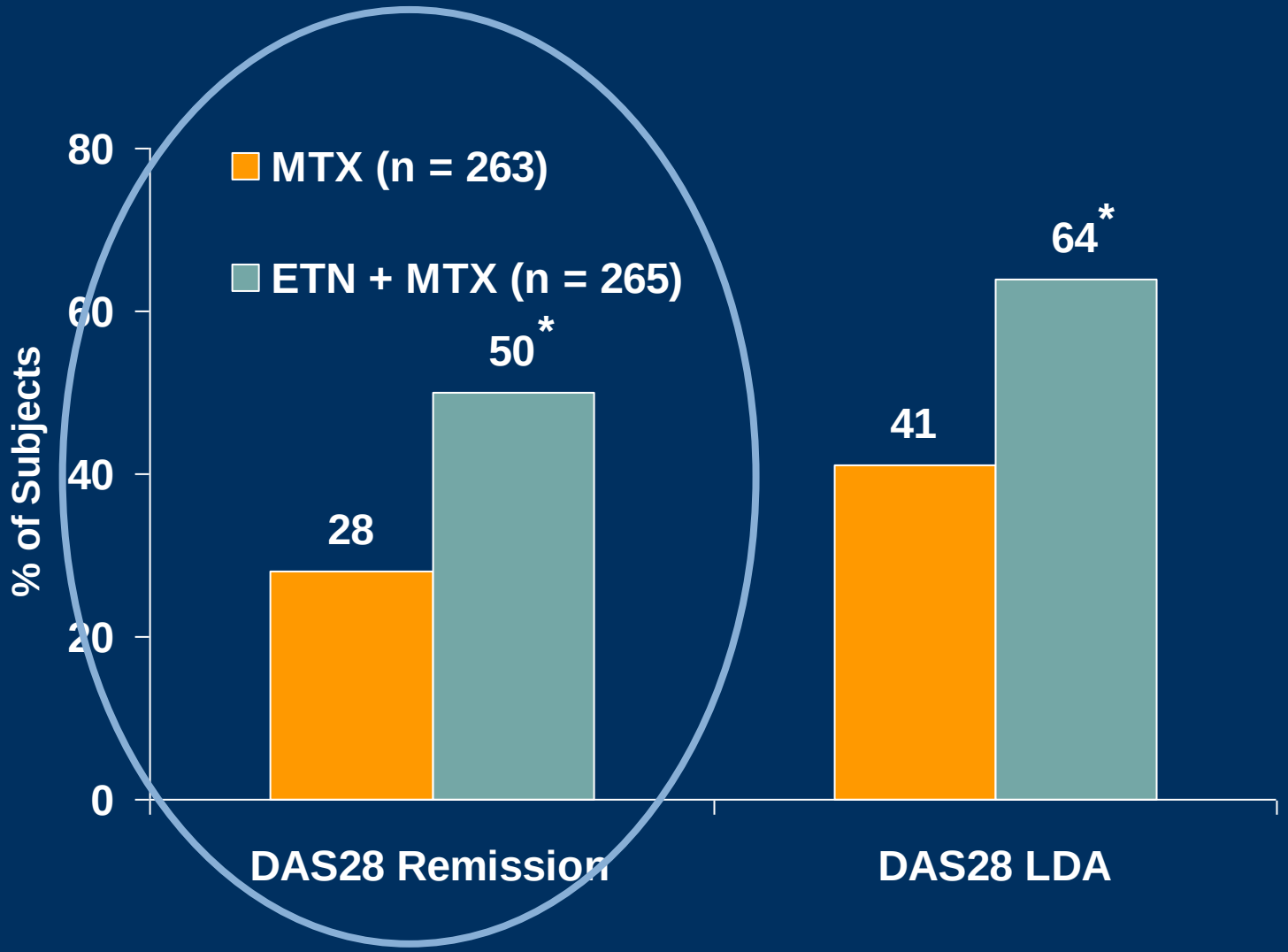
Cumulative Work Days Missed



*$P < 0.05$
Subjects working at baseline MTX, n = 100; E + MTX, n = 101

Menu

DAS28 Remission and Low Disease Activity at Week 52



*$P < 0.001$

Menu

MCQ 2

Ms RA was started on DMARDs by her rheumatologist. In the initial phase while her disease is still active, which one of the following is the best course of action to ensure optimal outcome?

a) The frequency of follow up should be according to the clinical judgement of her rheumatologist; and therapy adjusted only after 3 months
b) The frequency of follow up should be monthly; and therapy adjusted according to disease activity score at each visit
c) The frequency of follow up should be monthly; and therapy adjusted according to ultrasound finding
d) The frequency of follow up should be monthly; and therapy adjusted based on ESR and CRP readings
e) The frequency of follow up should be followed monthly; and therapy adjusted according to patient's symptoms.

Lesson # 2

Close monitoring and tight control is key to good outcome in RA

Intensive DMARD therapy improves disease activity in RA

Routine DMARD therapy

(n=55)

DMARD monotherapy
(active synovitis/ treatment failure)

⇩

Alternative monotherapy

⇩

+ 2nd DMARD

⇩

+3rd DMARD

Intensive DMARD therapy

(n=55)

Sulfasalazine
(increasing dose)

⇩

Triple therapy
(sulfasalazine + **methotrexate** + **folic acid** + **hydrochloroquine**)

⇩

Triple therapy
(**increasing methotrexate**)

⇩

Triple therapy
(**increasing sulfasalazine**)

⇩

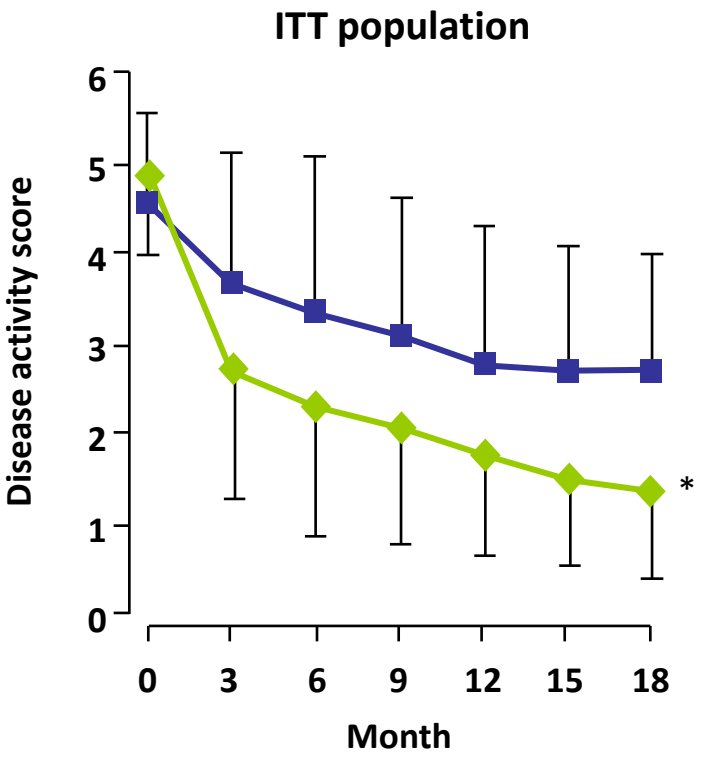
+ prednisolone

⇩

Change triple therapy
(**ciclosporin** + methotrexate + folic acid)

⇩

Change to alternative DMARD
(**leflunomide** or **sodium aurothiomalate**)

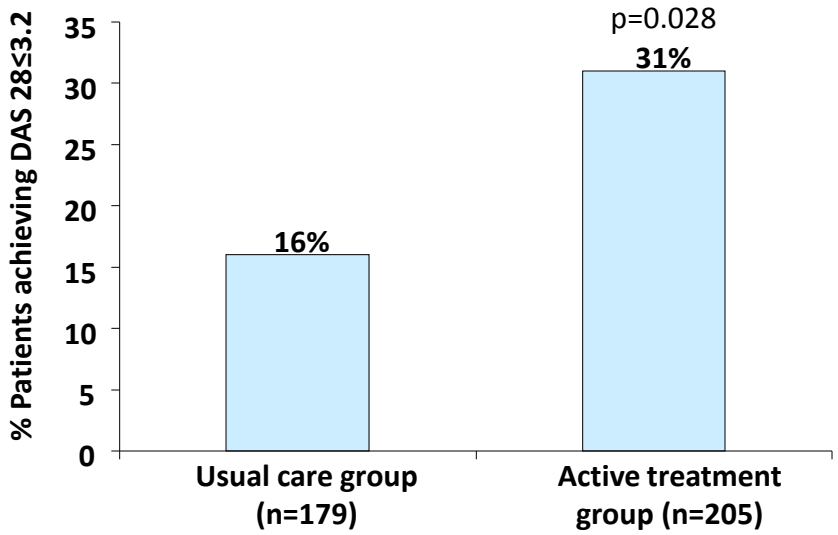


*p<0.0001 vs routine therapy after month 3

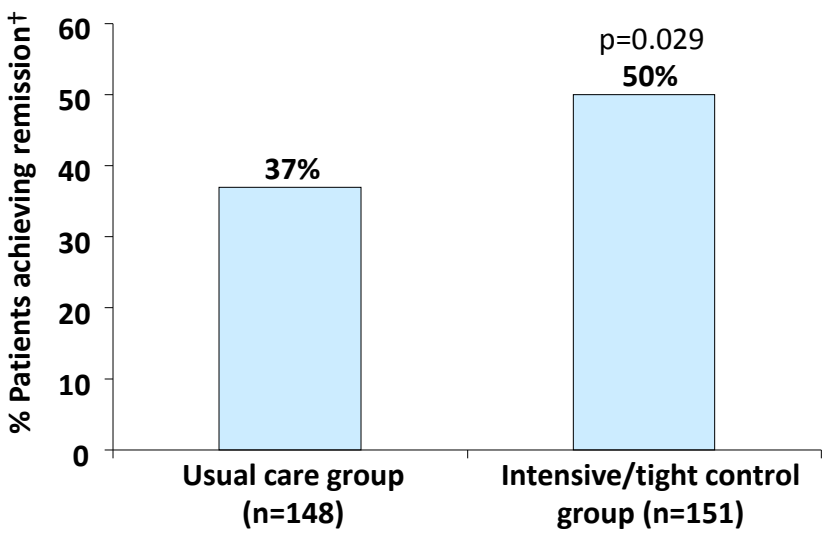
Adapted from Grigor C et al. Lancet 2004;364:263-269.

Tight monitoring of therapy improves outcomes in RA

ITT population (LOCF)[1]



ITT population (LOCF)[2]



Assessment/ measurement frequency	No systematic monitoring	Monitoring at 0, 4, 12 and 24 weeks	Monitoring every 3 months	Monitoring monthly
Active treatment	Cox-2 inhibitors, DMARDs, oral steroids allowed		Methotrexate monotherapy followed by combination methotrexate/cyclosporin, oral steroids not allowed	
Target	DAS 28≤3.2		Remission†	

LOCF=last observation carried forward.

*Remission defined as no swollen joints, and at least two of the following criteria: number of tender joints ≤3, erythrocyte sedimentation rate ≤20mm/hour and VAS general well-being ≤20mm for at least 3 months at any time during the 2 year trial.

1. Fransen J et al. Ann Rheum Dis 2005;64:1294–1298. 2. Verstappen SMM et al. Ann Rheum Dis 2007;66:1443–1449.

Treating rheumatoid arthritis to target: recommendations of an international task force

Josef S Smolen,[1,2] Daniel Aletaha,[1] Johannes W J Bijlsma,[3] Ferdinand C Breedveld,[4] Dimitrios Boumpas,[5] Gerd Burmester,[6] Bernard Combe,[7] Maurizio Cutolo,[8] Maarten de Wit,[9] Maxime Dougados,[10] Paul Emery,[11] Alan Gibofsky,[12] Juan Jesus Gomez-Reino,[13] Boulos Haraoui,[14] Joachim Kalden,[15] Edward C Keystone,[16] Tore K Kvien,[17] Iain McInnes,[18] Emilio Martin-Mola,[19] Carlomaurizio Montecucco,[20] Monika Schoels,[2] Desirée van der Heijde,[4] for the T2T Expert Committee

Smolen JS, et al. Ann Rheum Dis 2010;69:631–7

Treat to Target (T2T) Overarching Principle

- Treatment of RA must be based on a shared decision between patient and rheumatologist
- The primary goal of treating the patient with RA is to maximize long-term HRQoL through control of symptoms, prevention of structural damage, normalisation of function and social participation
- Abrogation of inflammation is the most important way to achieve these goals
- Treatment to target by measuring disease activity and adjusting therapy accordingly optimises outcomes in RA

Smolen JS, et al. Ann Rheum Dis 2010;69:631–7

Instruments of Measurement of RA disease activity

Table 3. Instruments to measure rheumatoid arthritis disease activity and to define remission

Instrument	Thresholds of disease activity levels
Patient Activity Scale (PAS) or PAS-II (range 0–10) (31)	Remission: 0–0.25 Low activity: 0.26–3.7 Moderate activity: 3.71 to <8.0 High activity: ≥8.0
Routine Assessment of Patient Index Data 3 (range 0–10) (42)	Remission: 0–1.0 Low activity: >1.0 to 2.0 Moderate activity: >2.0 to 4.0 High activity: >4.0 to 10
Clinical Disease Activity Index (range 0–76.0) (43)	Remission: ≤2.8 Low activity: >2.8 to 10.0 Moderate activity: >10.0 to 22.0 High activity: >22
Disease Activity Score in 28 joints (range 0–9.4) (44)	Remission: <2.6 Low activity: ≥2.6 to <3.2 Moderate activity: ≥3.2 to ≤5.1 High activity: >5.1
Simplified Disease Activity Index (range 0–86.0) (45)	Remission: ≤3.3 Low activity: >3.3 to ≤11.0 Moderate activity: >11.0 to ≤26 High activity: >26

2012 ACR RA Treatment Recommendations

Table 1. Disease activity indices: calculation and cutpoints of disease activity categories.

Index	Formula	Cutpoints
DAS-28	$0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \text{lognat}(ESR) + 0.014 \times GH$	$<2.6/<3.2/<5.1$*
SDAI	$SJC28 + TJC28 + PGA + EGA + CRP$	$\leq 3.3/\leq 11/\leq 26$
CDAI	$SJC28 + TJC28 + PGA + EGA$	$\leq 2.8/\leq 10/\leq 22$

Abbreviations: DAS: Disease Activity Score;DAS-28: DAS based on a 28 joint count; CRP, C-reactive protein; EGA, evaluator global assessment of disease activity; ESR, erythrocyte sedimentation rate; GH, global health; PGA, patient global assessment of disease activity; SJC, swollen joint count; TJC, tender joint count.

* Remission vs. Low disease activity/low vs. moderate disease activity/moderate vs. high disease activity GH in mm VAS; SDAI: CRP in mg/dl; SDAI, CDAI: PGA, EGA in cm on a Visual Analogue Scale (VAS).

ARTHRITIS & RHEUMATISM
Vol. 63, No. 3, March 2011, pp 573–586
DOI 10.1002/art.30129

Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and wileyonlinelibrary.com

American College of Rheumatology/European League Against Rheumatism Provisional Definition of Remission in Rheumatoid Arthritis for Clinical Trials

Table 6. American College of Rheumatology/European League Against Rheumatism definitions of remission in rheumatoid arthritis clinical trials*

Boolean-based definition:
At any time point, patient must satisfy all of the following:
Tender joint count ≤1†
Swollen joint count ≤1†
C-reactive protein ≤1 mg/dl
Patient global assessment ≤1 (on a 0–10 scale)‡
Index-based definition:
At any time point, patient must have a
Simplified Disease Activity Index score of ≤3.3§

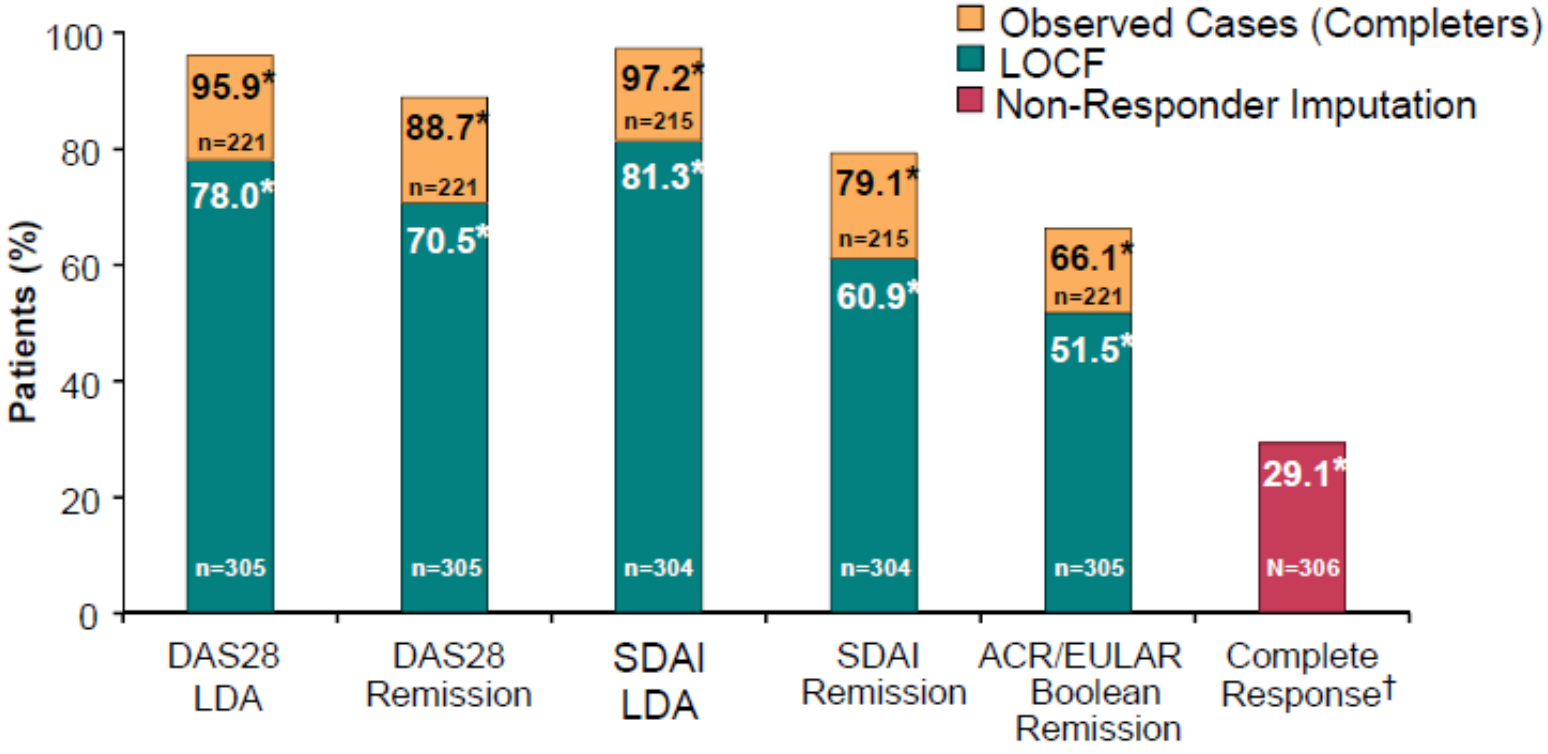
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sustained Remission with Etanercept Tapering in Early Rheumatoid Arthritis

Paul Emery, F.R.C.P., Mohammed Hammoudeh, M.D., Oliver FitzGerald, M.D., Bernard Combe, M.D., Ph.D., Emilio Martin-Mola, M.D., Ph.D., Maya H. Buch, M.B., Ch.B., Ph.D., Marek Krogulec, M.D., Theresa Williams, P.A., M.S., Stefanie Gaylord, B.S.N., Ronald Pedersen, M.S., Jack Bukowski, M.D., Ph.D., and Bonnie Vlahos, M.B.A., R.N.

LDA, Remission, and Complete Response at Week 52



*P<0.0001 vs baseline.
†Complete response=achievement of DAS28 <2.6, HAQ ≤0.5, and ΔmTSS ≤0 over 52 weeks. Non-responder imputation was used to handle missing data.
SDAI, simplified disease activity index; LOCF, last observation carried forward.

Is Clinical Remission in RA patient true remission?

- MRI and US detected synovitis in the majority of patients with clinical remission

Brown et al A & R 2006

- In patients in clinical remission, MRI and US synovitis predict subsequent erosive progression on conventional radiography

Brown et al A & R 2008

MCQ 3

- Ms RA was treated with DMARDs and she was in complete remission at the end of one year. Which of the following is the appropriate course of action?
  a. She should continue DMARDs, NSAID and steroids indefinitely
  b. She should taper her DMARDs but maintained on systemic steroids and NSAID
  c. She should taper her DMARDs once systemic steroids and NSAID are stop
  d. She should stop systemic steroids, NSAID and DMARDs together
  e. She should only stop steroids

Lesson # 3

Drug Free Remission is possible in RA!

BeSt

Comparing Four Treatment Strategies Using Tight Control Based on DA

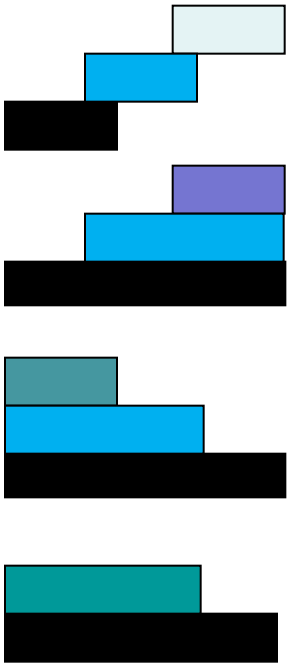
Studying Treatment Strategy

Comparison of four treatment strategies
Using dynamic disease management

508 Patients

Disease Duration ≤2 years

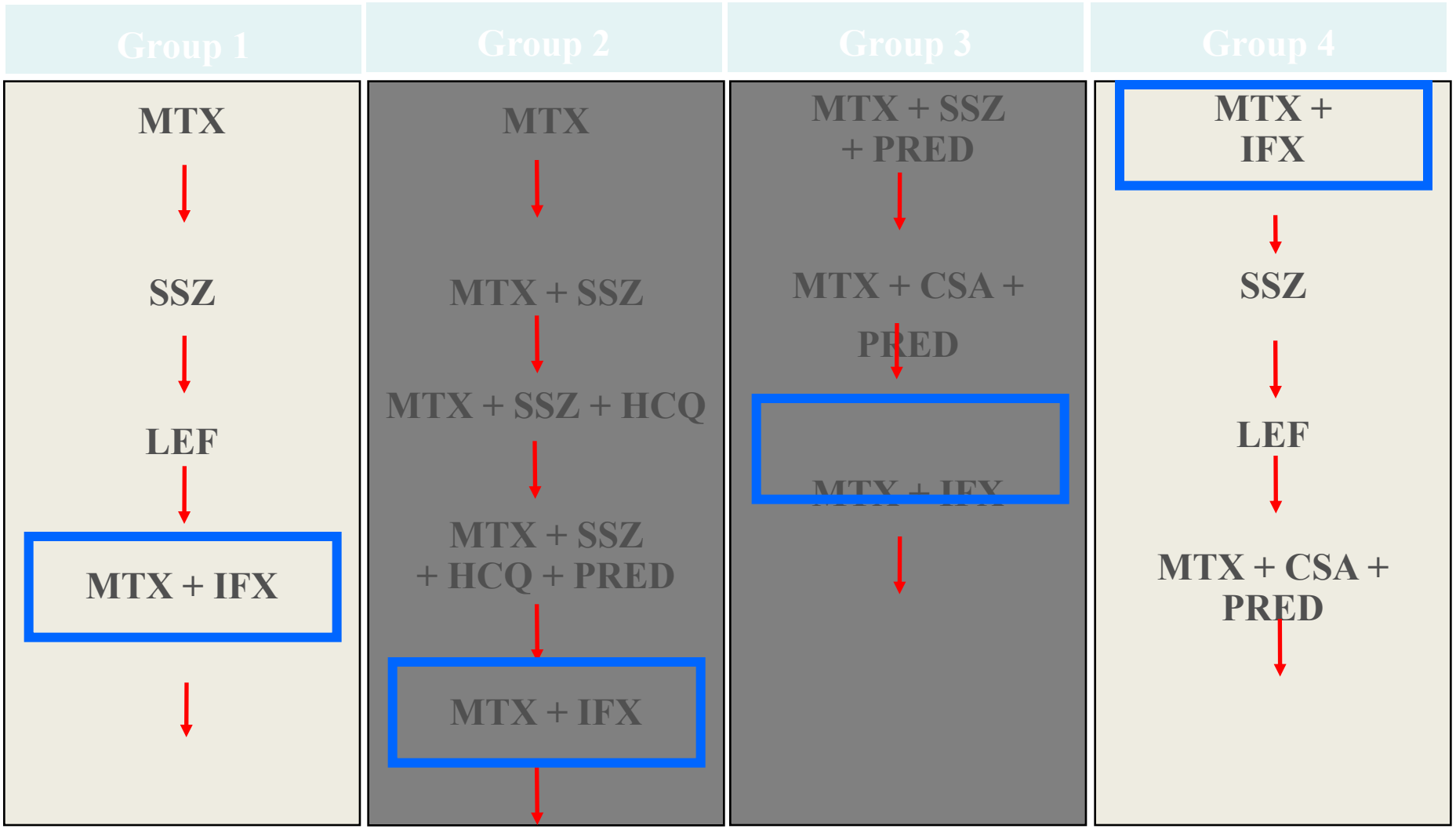
Active Disease



1. Sequential monotherapy (n=126)
2. Step-up combination therapy (n=121)
3. Initial combination therapy (COBRA) (n=133)
4. Initial combination with IFX (n=128)

Goekoop-Ruiterman YPM et al. Arthritis Rheum 2005;52:3381-3390.

Treatment Strategies in eRA



LEF: Leflunomide; HCQ: Hydroxychloroquine; CSA: Cyclosporine

Goekoop-Ruiterman YPM et al. Arthritis Rheum 2005;52:3381-3390.

Treatment Strategies in the BeSt Study

Maximal success through 2 to 3-monthly treatment-adjustments based on DAS44-scores:

DAS44 >2.4 → next step

DAS44 ≤2.4 → continue therapy

Two consecutive assessments

DAS44 ≤2.4 → step back/taper

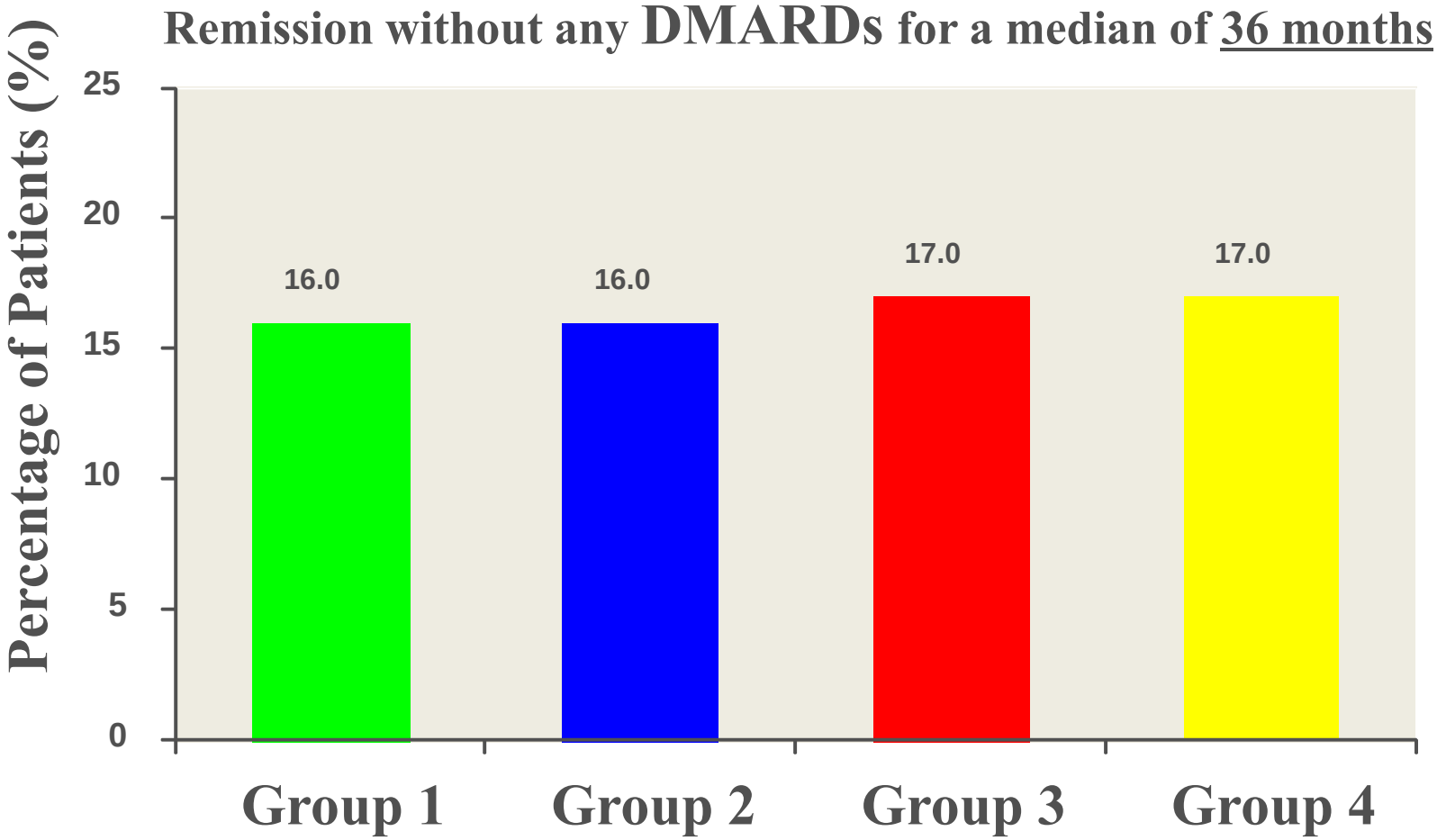
Goekoop-Ruiterman YPM et al. Arthritis Rheum 2005;52:3381-3390.

Outcomes

- Primary endpoints
  - Functional outcomes (HAQ)
  - Radiographic joint damage (Sharp-Van der Heijde score / SHS)
- Secondary endpoints
  - Clinical remission (DAS44<1.6)
  - ACR 20, 50, 70

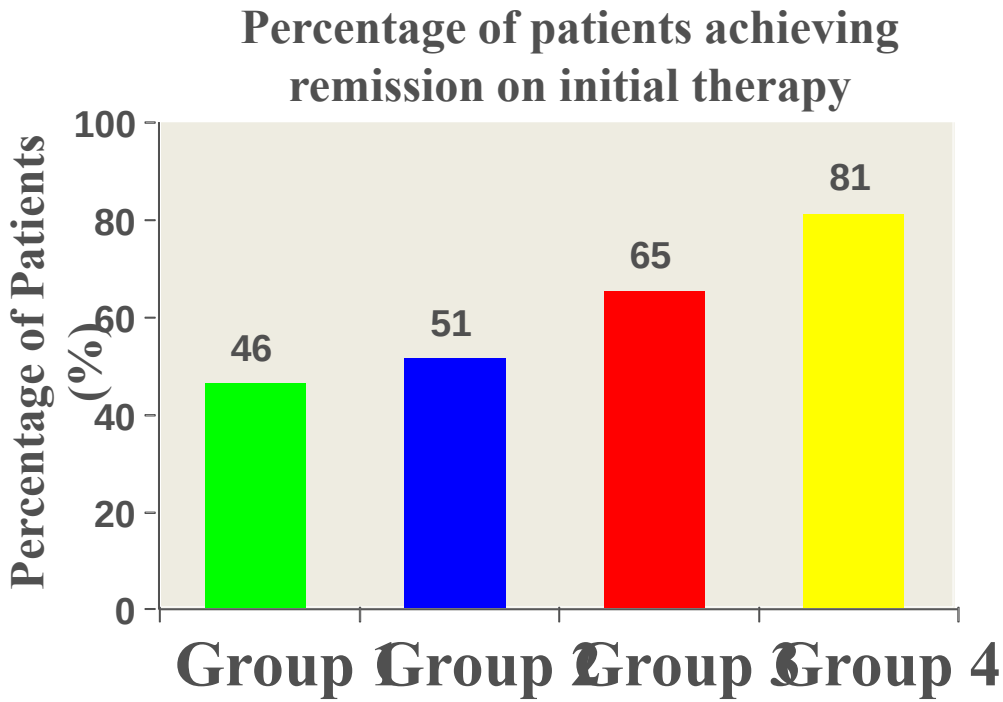
Goekoop-Ruiterman YPM et al. Arthritis Rheum 2005;52:3381-3390.

Sustained Drug-free Remission at 7 Years



Adapted from Dirven et al. ACR 2010. Abstract 334.

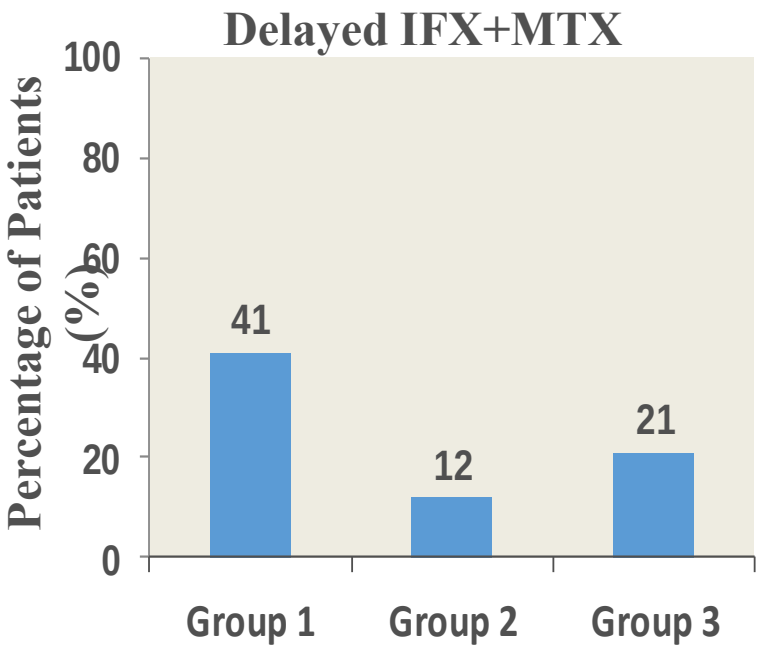
5 Year Results: Remission**



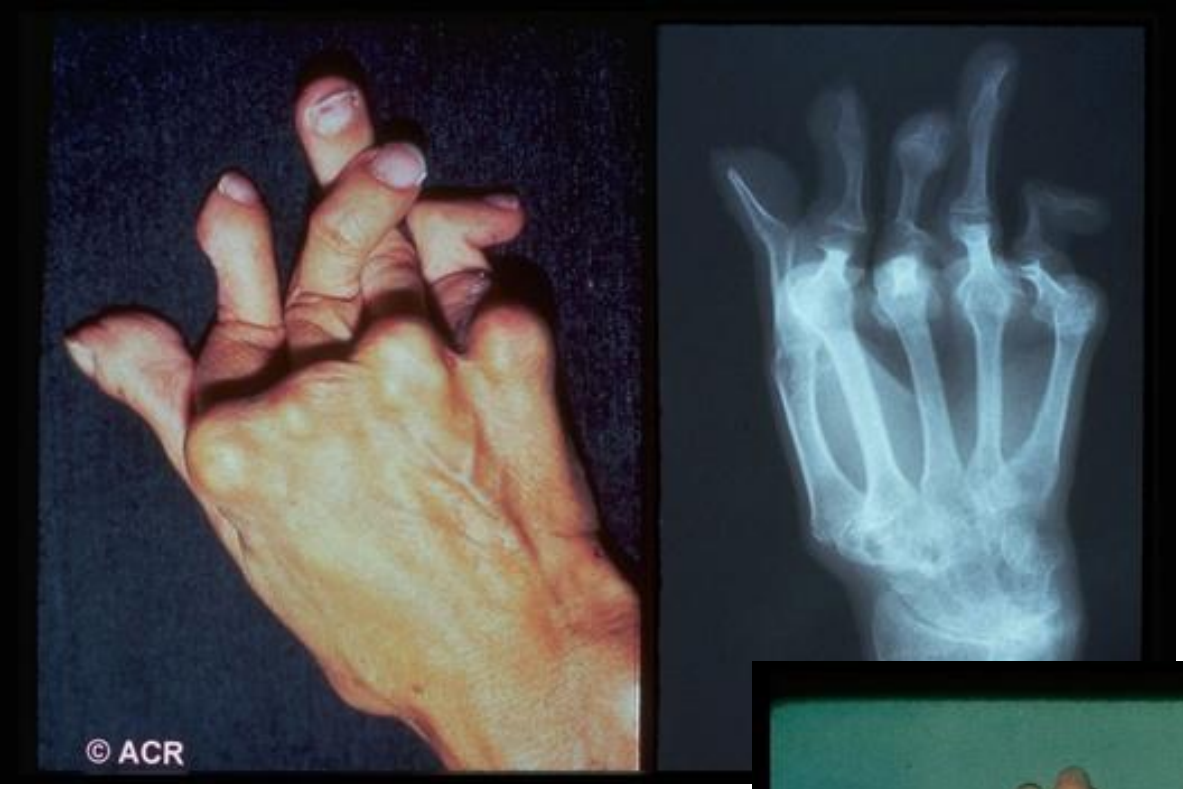
With DAS-steered, tight-controlled treatment, 48% of all patients achieved remission and 14% drug-free remission

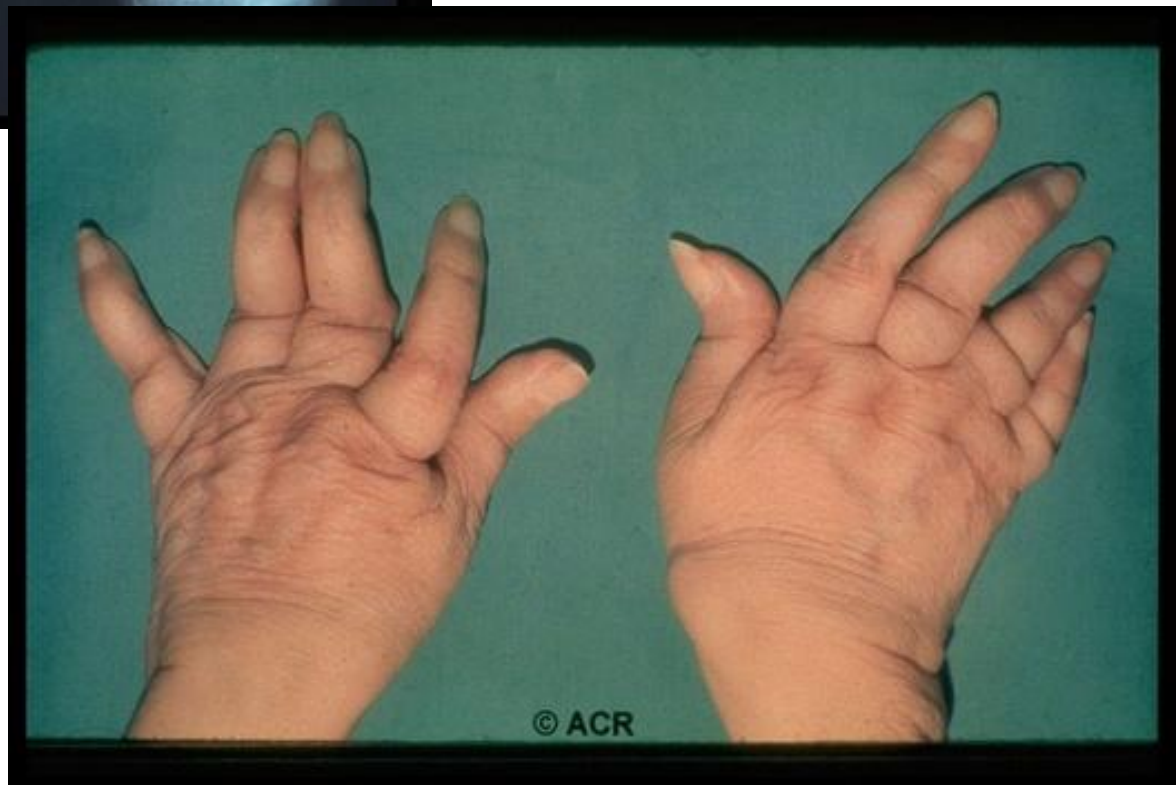
**DAS<1.6

Includes remission and drug-free remission



Adapted from Klarenbeek et al. Ann Rheum Dis 2011; epub March 17th(10.1136/ard.2010.141234).


© ACR


© ACR

Thank you