Πρώιμη έναρξη της βιολογικής θεραπείας στη ρευματοειδή αρθρίτιδα.

Υπάρχει επαρκής βιβλιογραφική τεκμηρίωση?

ΑΝΤΙΛΟΓΟΣ

Κυριακή Μποκή

Μεσσηνία 24-6-2011

Στρατηγική θεραπείας ρευματοειδούς αρθρίτιδας

Πρώιμη θεραπευτική παρέμβαση

«Εντατική» παρακολούθηση

Καθορισμός αντικειμενικών στόχων θεραπείας

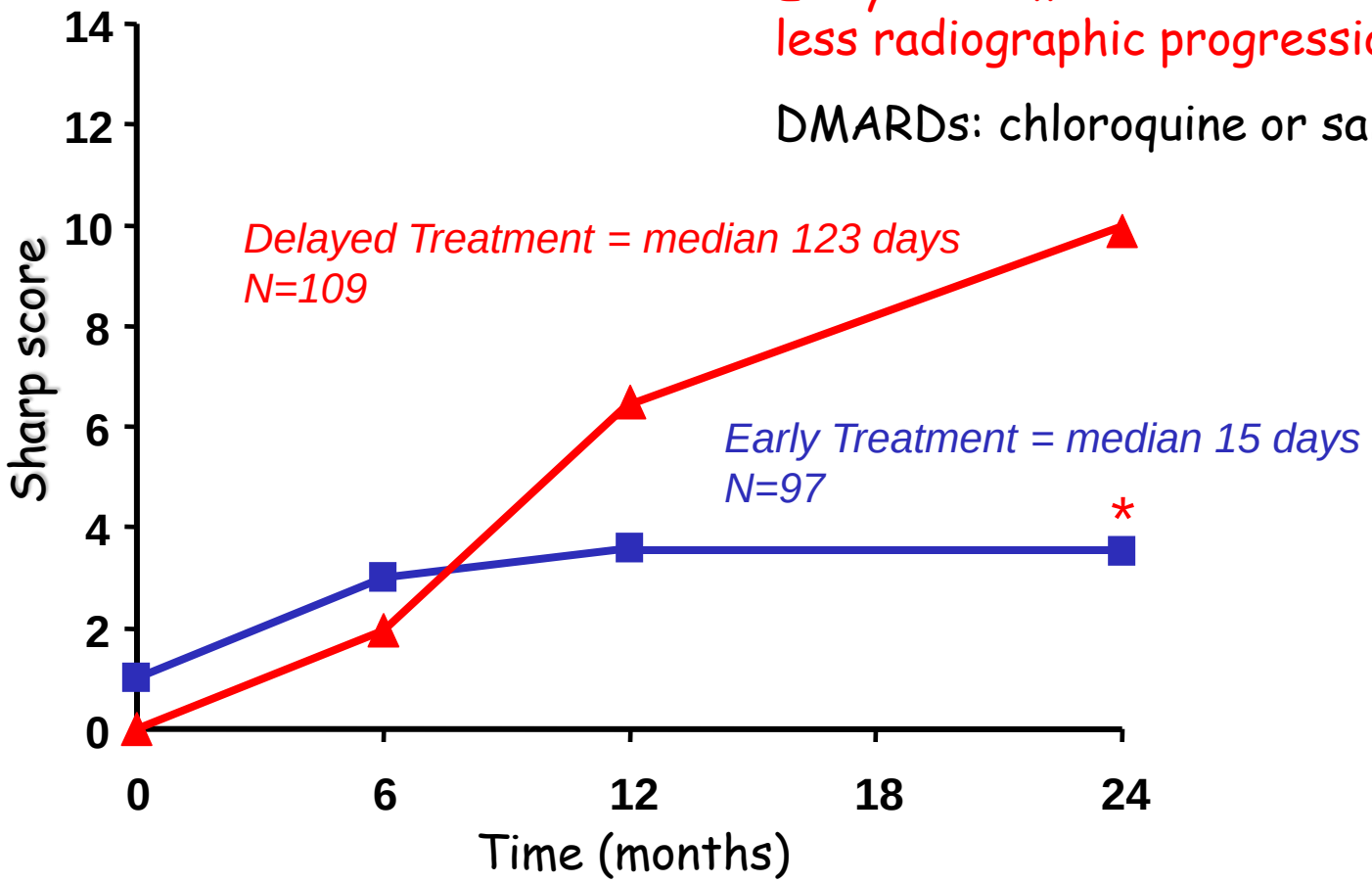
Συνδυασμός φαρμάκων

Early treatment

Πρώιμη θεραπευτική παρέμβαση

Early treatment is associated with less radiographic progression

DMARDs: chloroquine or salazopyrine



* p<0.05 compared with delayed treatment group

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

Πώς επιτυγχάνονται οι θεραπευτικοί στόχοι;

Table 1 Characteristics of the tight control studies

Study	Interventions/groups	n	Medication at the start	Frequency of assessment	Inclusion criteria	Disease duration
FIN-RACo	Combination therapy*	97	SSZ, MTX, HCQ, predn	3 months (variable)	ARA criteria RA, 18–65 yr, symptoms <2 yr, active disease ⩾3 SJ and 3 of: ⩾28 mm/h ESR or ⩾19 mg/l CRP, ⩾29 min/ms, >5 SJ or >10 TJ	<2 yr
	Mono therapy	98	SSZ ± predn	3/6 months (clinical decision/variable)		
TICORA	Intensive management*	55	DMARD, i.a. steroid	1 month (DAS)	18–75 yr, disease duration <5 yr, active disease (DAS>2.4)	<5 yr
	Routine management	55	DMARD mono	3 months (clinical decision)		
BeSt	Sequential mono therapy*	126	MTX	3 months (DAS44)	ACR criteria RA, ⩾18 yr, disease duration ⩽2 yr, active disease: ⩾6 of 66 SJ, ⩾6 of 68 TJ, ⩾28 mm/h ESR, ⩾20 mm VAS global health	⩽2 yr
	Step-up combination therapy*	121	MTX	3 months (DAS44)		
	Initial combination therapy + h.d. predn*	133	MTX, SSZ, predn	3 months (DAS44)		
	Initial combination therapy + infliximab*	128	MTX, infliximab	3 months (DAS44)		
CAMERA	Intensive strategy group*	151	MTX	1 month (computer decision program)	ACR criteria RA, >16 yr, early RA (<1 yr)	<1 yr
	Conventional strategy group	148	MTX	3 months (clinical decision)		

Bakker MF, et al. Ann Rheum Dis 2007;66 (Suppl III):iii56–iii60

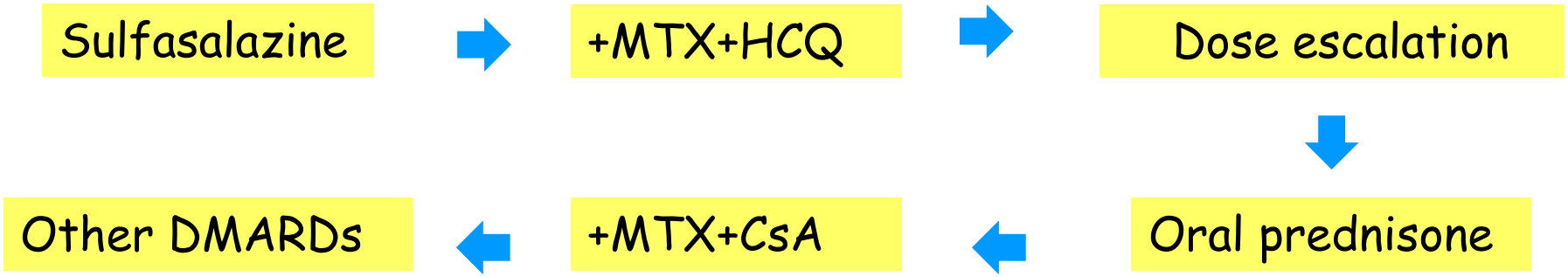
Tight control Αποτελεσματικότητα της συστηματικής παρακολούθησης βάσει του DAS

TICORA

Single-blind, 18-month, controlled trial, including 110 patients with RA <5 years, randomized to either intensive management of protocol-based escalation of DMARDs or routine care

Α. Εντατική παρακολούθηση

- Εκτίμηση DAS /μήνα
- DAS >2.4 → ↑ DMARDs

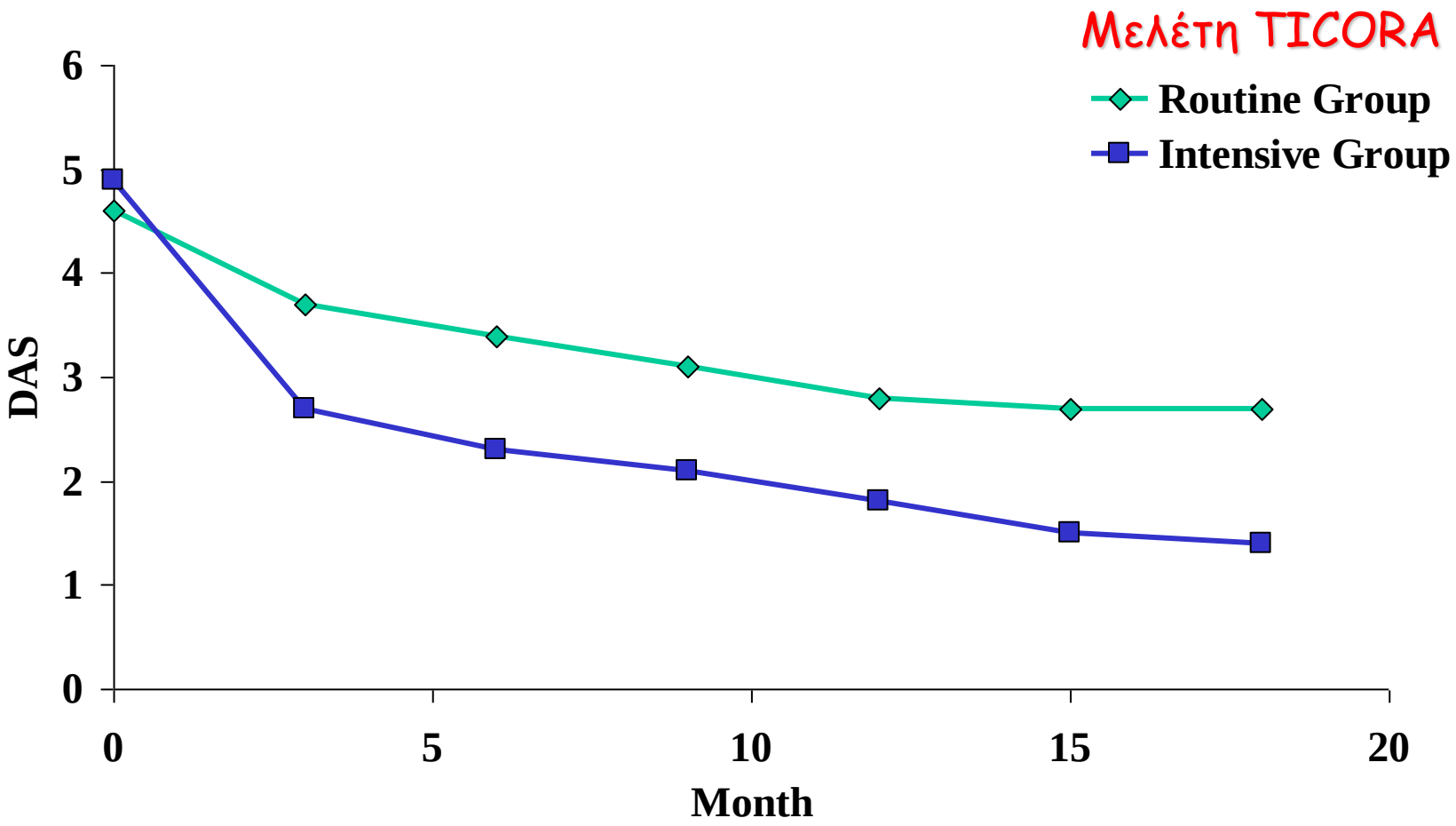


Β . Συνήθης παρακολούθηση

- Εκτίμηση /3μήνες
- Τροποποίηση αγωγής βάσει της γνώμης του ιατρού

Grigor C, et al. Lancet. 2004;364(9430):263-9.

Αποτελεσματική η συστηματική παρακολούθηση και τροποποίηση της αγωγής βάσει του DAS



Grigor C, et al. Lancet. 2004;364(9430):263-9.

Κλινικά αποτελέσματα σε 18 μήνες

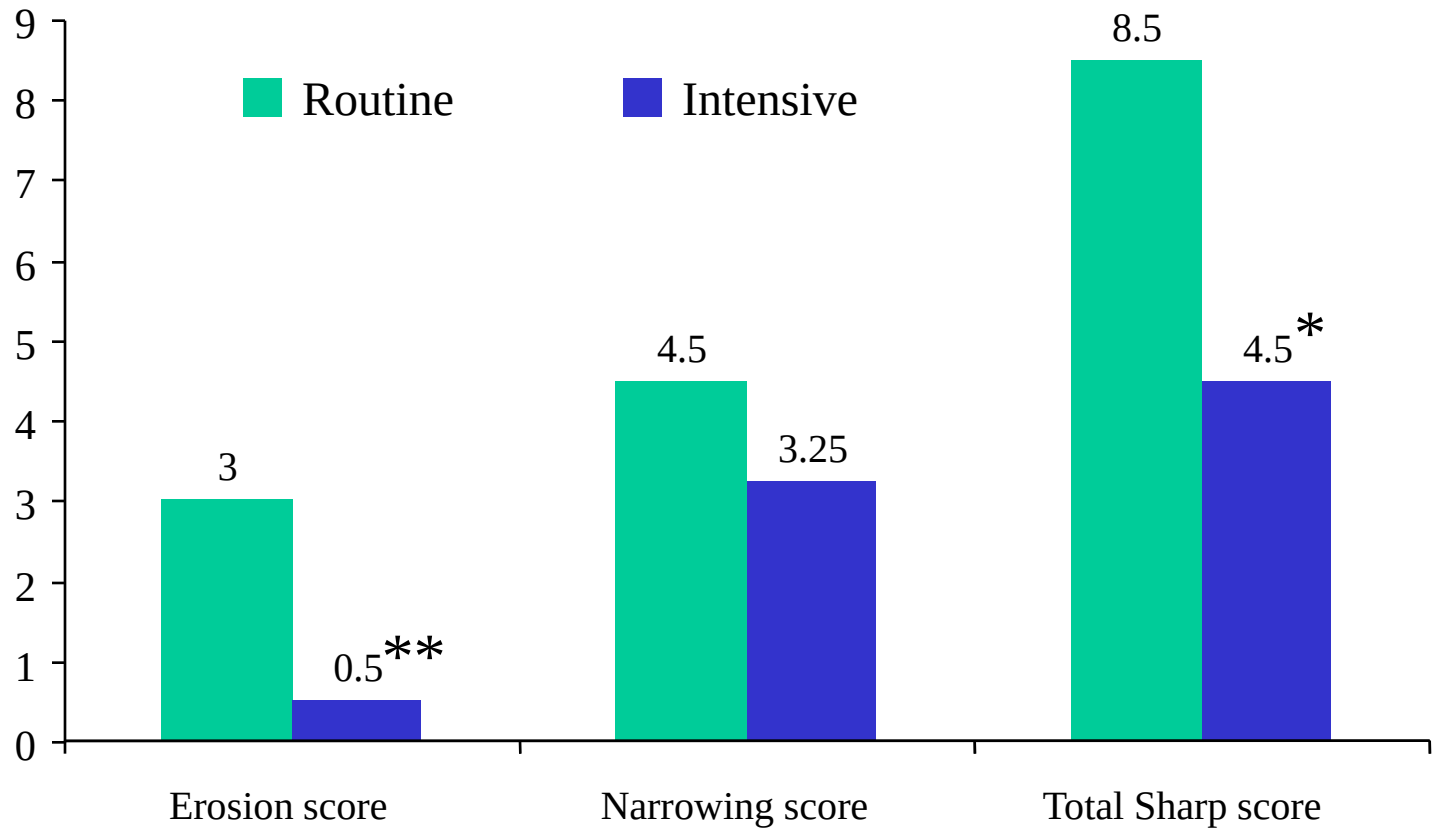
	Routine Care (n=53)	Intensive Care (n=50)	*P*-value
Mean Fall in DAS	-1.9	-3.5	*P*<0.0001
EULAR Good Response (DAS ≤2.4 and fall of 1.2 from baseline)	44%	82%	*P*<0.0001
EULAR Remission	16%	65%	*P*<0.0001
ACR50	40%	84%	*P*<0.0001
ACR70	18%	71%	*P*<0.0001
Change in CRP (mg/dL)	-14	-30	*P*=0.09
Change in HAQ	-0.47	-0.97	*P*=0.0025
SF12 Physical Summary Score	4.0	9.3	*P*=0.021

Εντατική παρακολούθηση και κλινικές μετρήσεις μειώνουν τη δραστηριότητα της νόσου

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

Ακτινολογική εξέλιξη: 0 και 18 μήνες

Median change in erosion, joint space narrowing and total Sharp score



* $P<0.02$, ** $P<0.002$, Mann-Whitney

Grigor C et al. Lancet 2004; 364: 263

Treatment Strategies in Early RA

BeSt

Target to treat

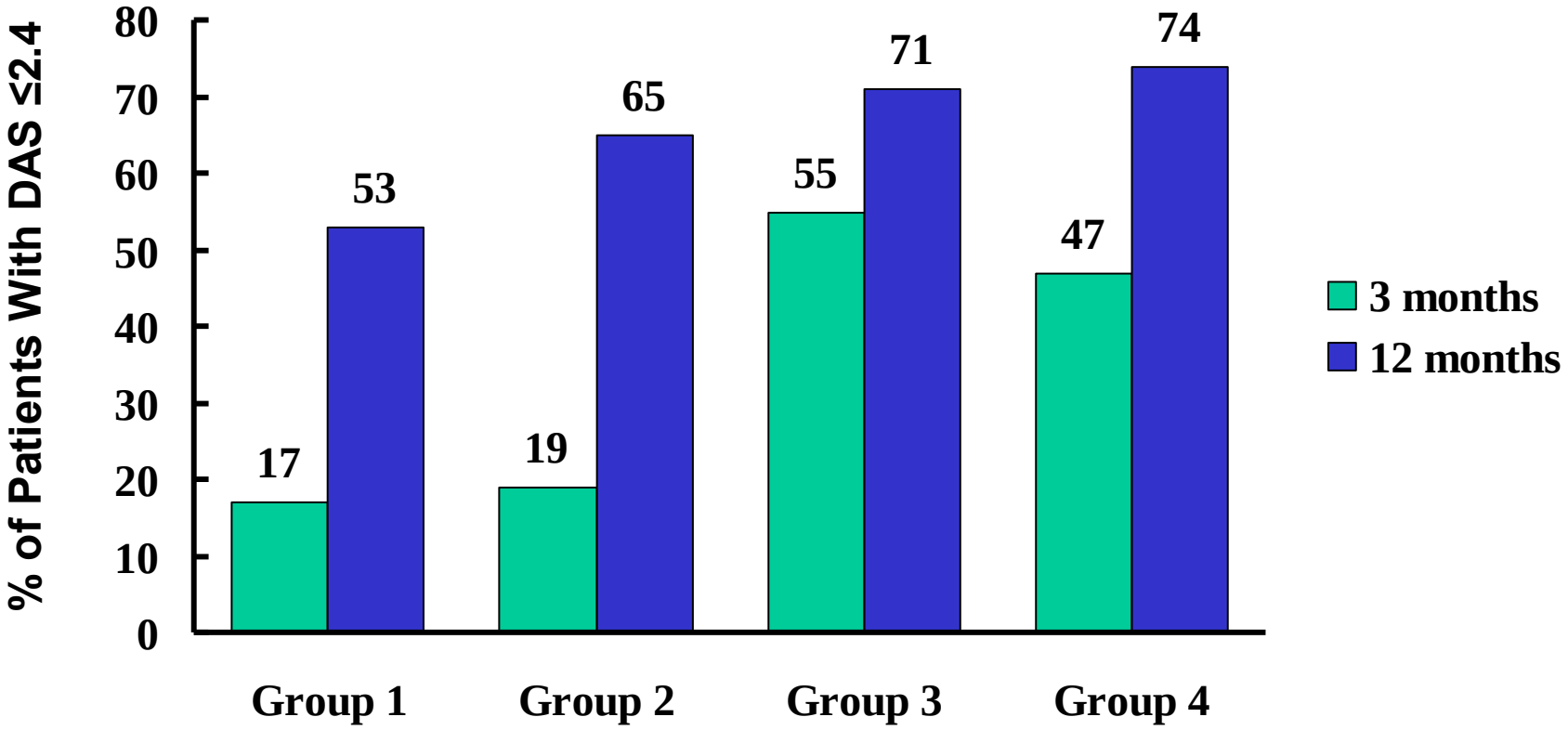
N=508

Treatment adjustments were made every 3 months in an effort to obtain low disease activity

	Sequential MONO-Therapy	STEP-UP Therapy	Initial COMBO Therapy	Initial BIOLOGIC Therapy
1.	MTX	MTX	MTX + SSZ + PRED	MTX + Infliximab
2.	SSZ	MTX + SSZ	MTX + CSA + PRED	SSZ
3.	LEF	MTX + SSZ + HCQ	MTX + Infliximab	LEF
4.	MTX + Infliximab	MTX + SSZ + HCQ + PRED		MTX + CSA + PRED
5.		MTX + Infliximab		

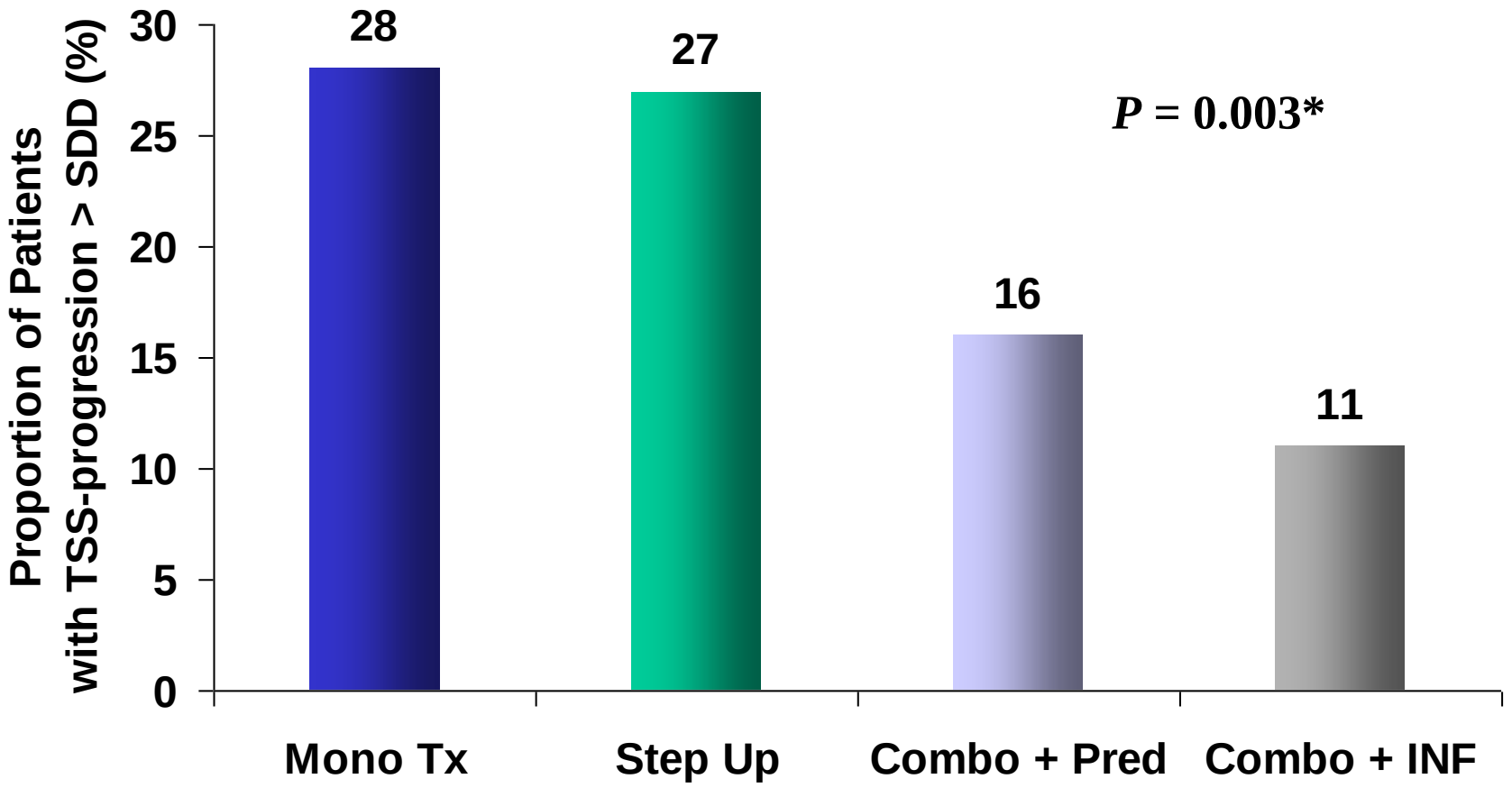
De Vries-Bouwstra JK, et al. Arthritis Rheum. 2003;48:3649.

DAS Responders: BeSt Study



De Vries-Bouwstra JK, et al. Arthritis Rheum. 2003;48:3649.

Ακτινολογική εξέλιξη στα 2 χρόνια

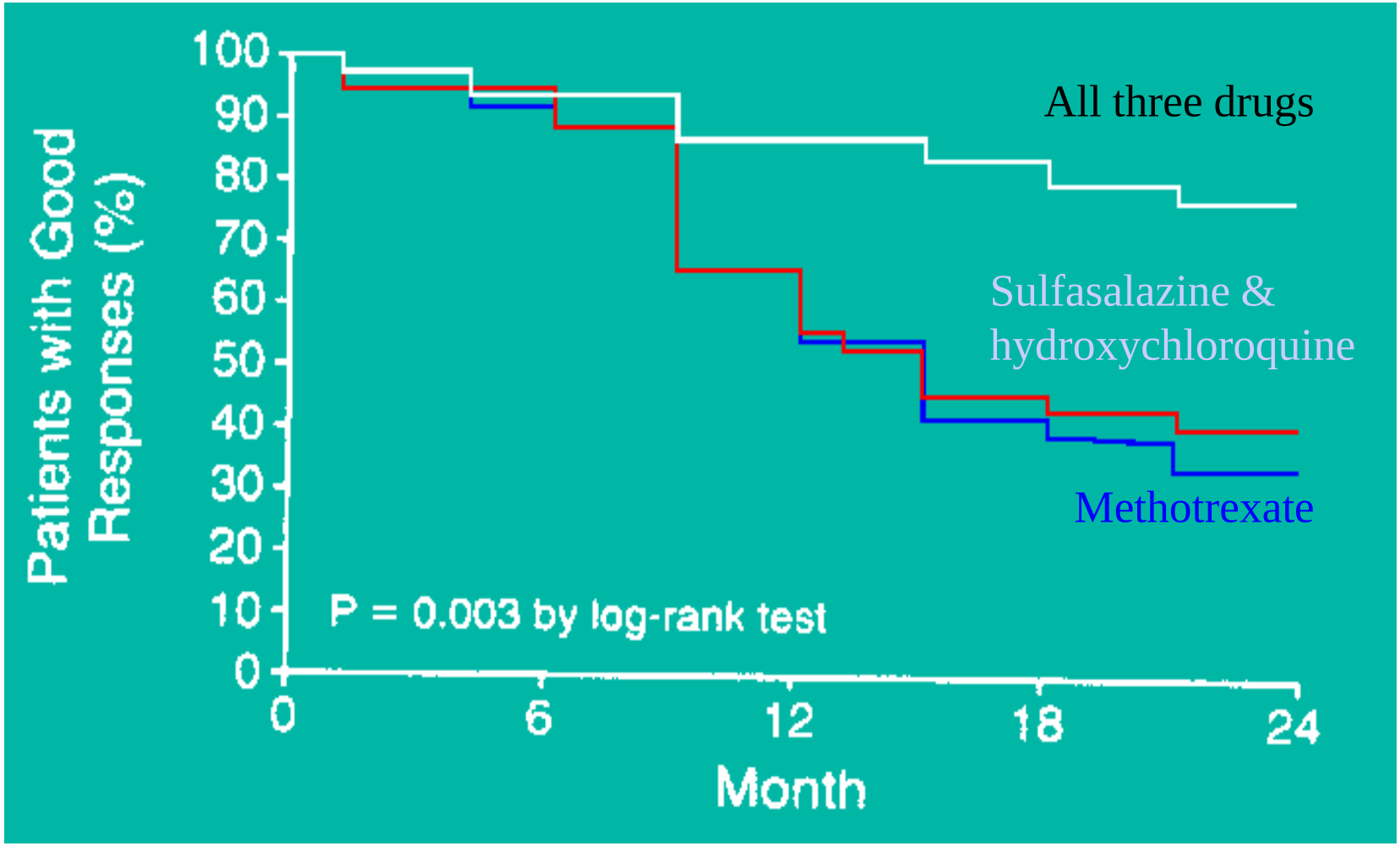


* Overall *P*-value, SDD = smallest detectable difference

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

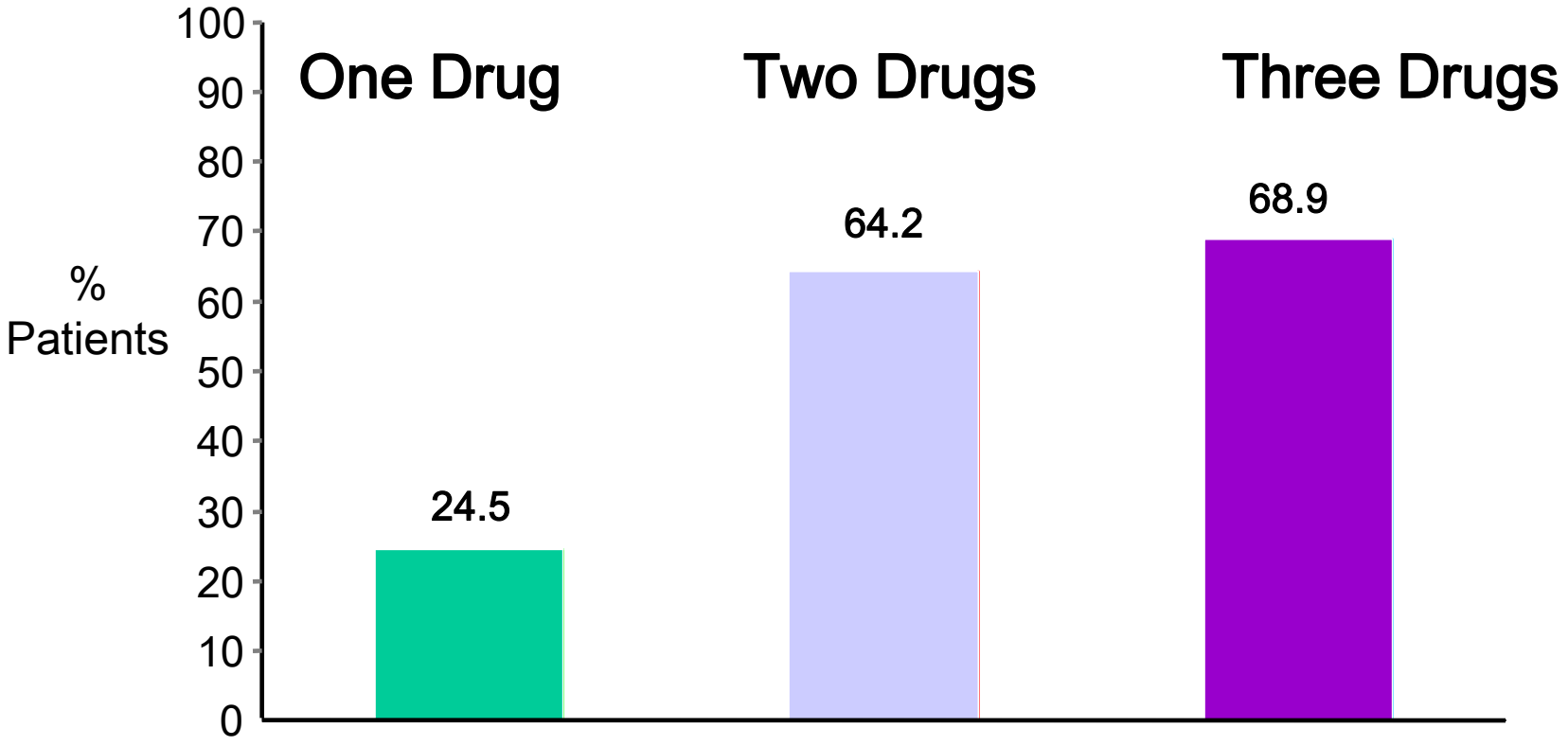
Monotherapy vs Combination therapy?

Treatment of RA with methotrexate alone, sulphasalazine and hydroxychloroquine, or a combination of all three medications



O'Dell JR et al N Eng J Med 1996;334:1287-1291

Combination Therapy in Early RA
No Radiographic Progression at 24 Months



Grp I: One drug: MTX or HCQ or SSZ Grp II: Two drugs : MTX + HCQ or MTX + SSZ

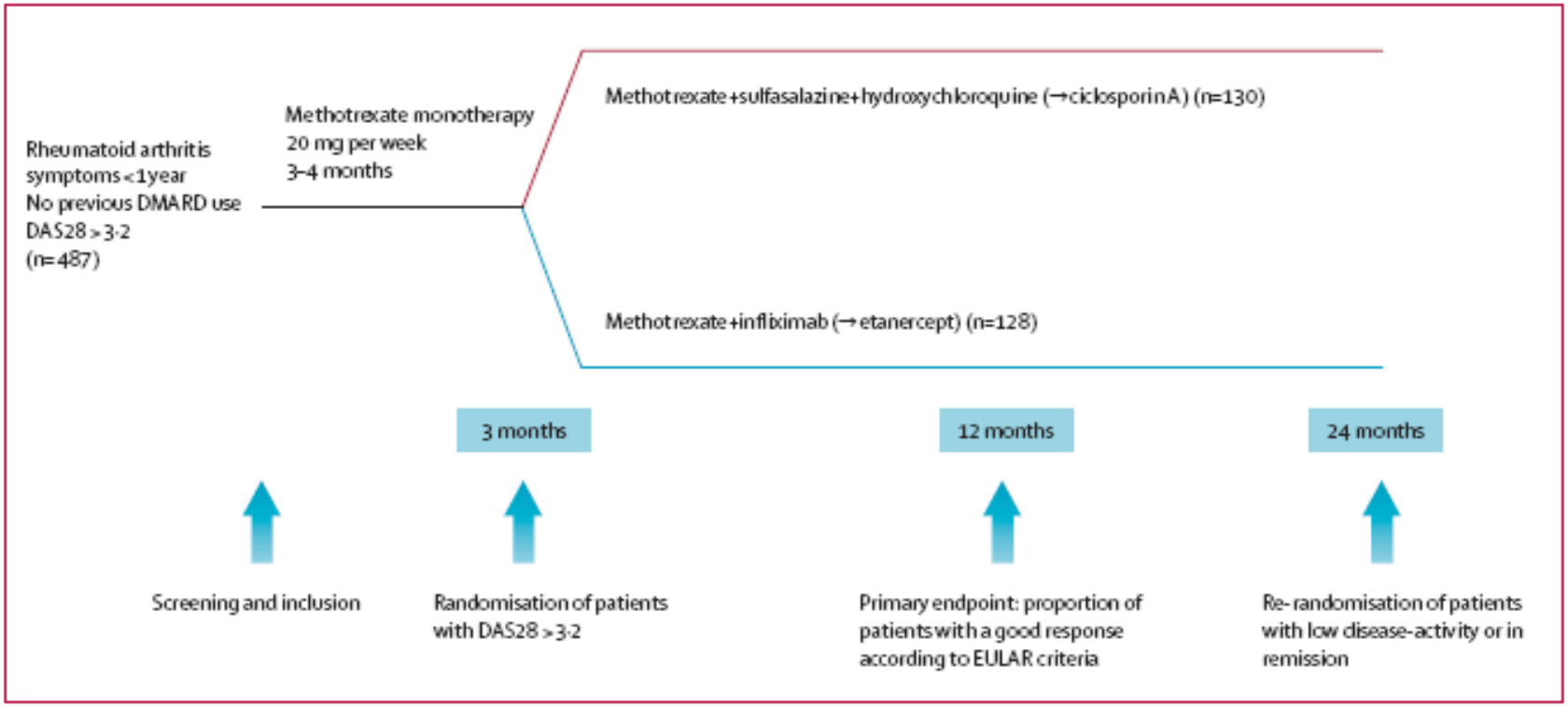
Grp III: Three drugs: MTX + HCQ + SSZ; I vs II (*P*=0.001); I vs III (*P*=0.001); II vs III (*P* NS)

Calguneri M, et al. Clin Exp Rheumatol. 1999;17:699-704.

Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial

R F van Vollenhoven, S Ernestam, P Geborek, I F Petersson, L Cöster, E Waltbrand, A Zickert, J Theander, Å Thörner, H Hellström, A Teleman, C Dackhammar, F Akre, K Forslind, L Ljung, R Oding, A Chatzidionysiou, M Wörnert, J Bratt

Lancet 2009; 374: 459–66



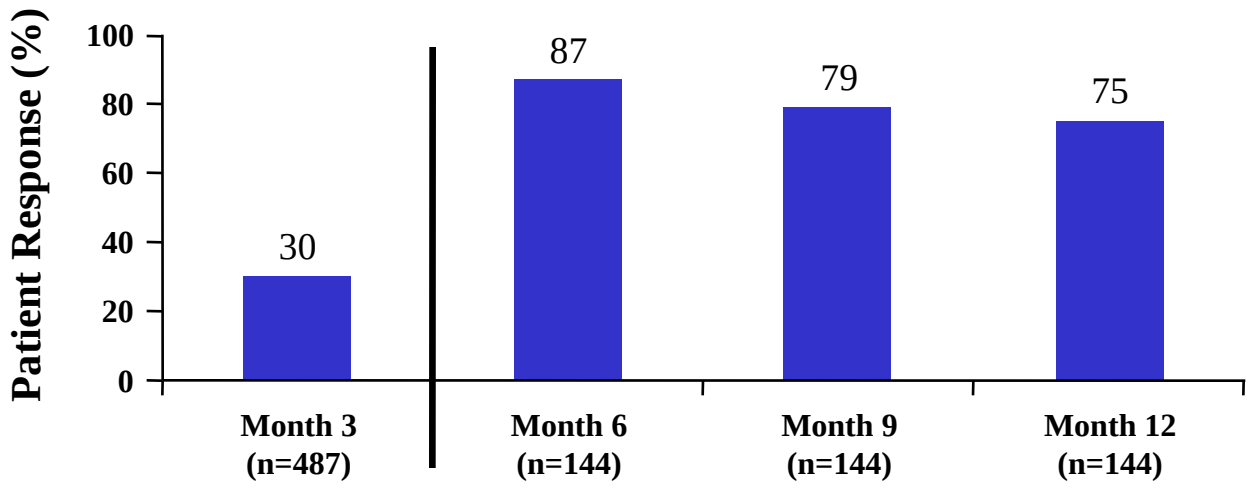
van Vollenhoven RF, et al. Lancet 2009; 374: 459-466

SWEFOT

Μονοθεραπεία με MTX σε πρώιμη PA οδηγεί σε LDA

- N=487 με πρώιμη PA (< 1 έτος)
- Σε όλους χορηγήθηκε MTX (έως 20 mg/week)
- Μετά 3-4 μήνες, 144 ασθενείς με DAS28<3.2 συνέχισαν με MTX & δεν συμμετείχαν στην ελεγχόμενη μελέτη SWEFOT

Patients on MTX Monotherapy with DAS28<3.2

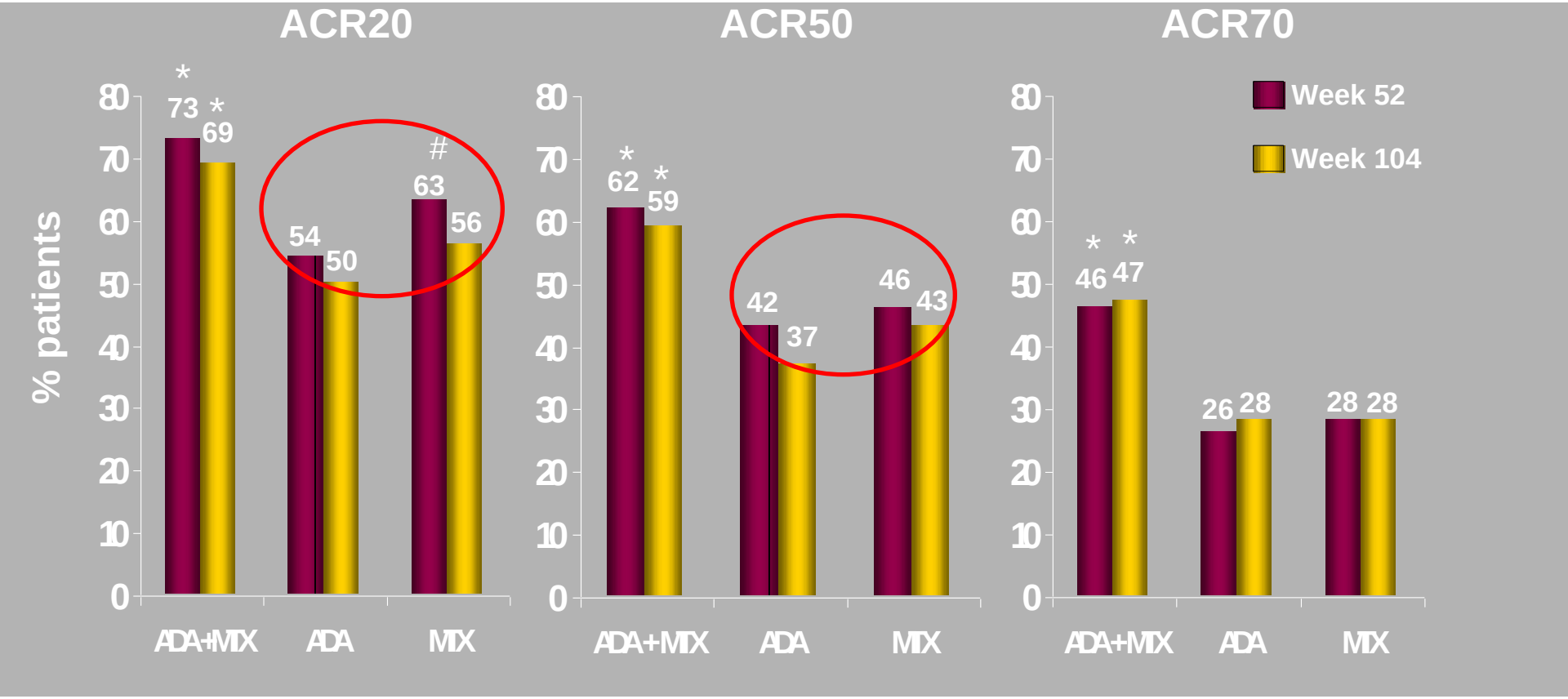


- **75% των ασθενών συνεχίζουν με MTX (μονοθεραπεία) με LDA (DAS28 <3.2)**

Van Vollenhoven RF, et al. Presented at: 2008 ACR Annual Scientific Meeting; October 24-29, 2008; San Francisco, CA. Abstract 717.

PREMIER Study

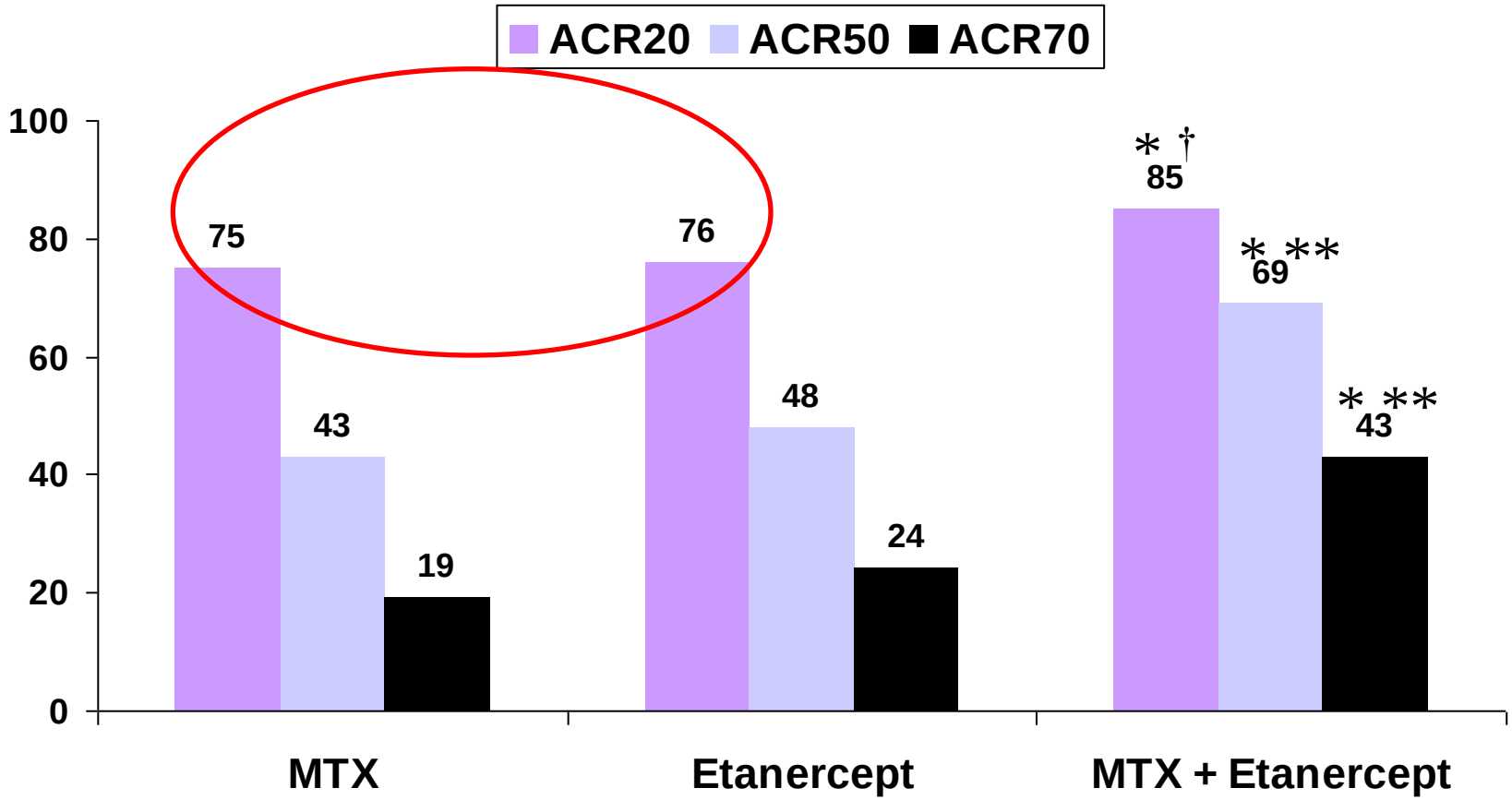
ACR 20/50/70 at Weeks 52 and 104



*p<0.001 for adalimumab + MTX *vs* MTX alone and adalimumab alone
p=0.043 for MTX vs adalimumab, others NS

Breedveld FC, et al. Arthritis Rheum. 2006;54:26-37.

TEMPO: Clinical Response at Week 52



*P<0.01 combination vs MTX; †P<0.05 combination vs etanercept; **P<0.01 combination vs etanercept

Klareskog L. *EULAR* 2003. Satellite Symposium: 'New Perspectives on Treatment Expectations in Rheumatoid Arthritis' Efficacy and Tolerability – Evolving Expectations for Biological Therapy in Rheumatoid Arthritis.

TEAR Trial: RCT in early RA

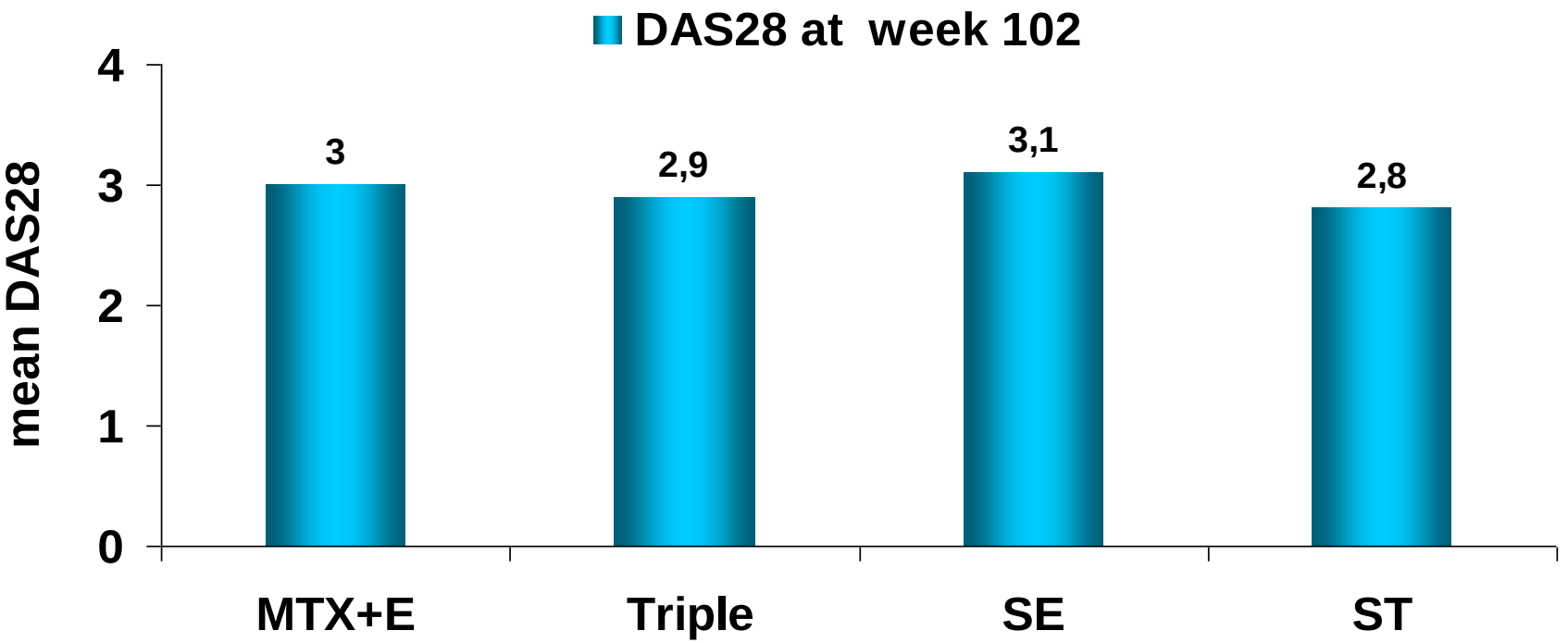
Immediate MTX+HCQ+SSZ (Triple Therapy)	Immediate MTX+ etanercept	Step up from MTX to triple therapy	Step up from MTX to MTX+etanercept

If DAS > 3.2 at 6 months

DAS28 at 2 years	**2.9**	**3.0**	**2.8**	**3.1**
ACR20 at 6 months (%)	64.0	63.6	47.7	45.2
ACR50 at 6 months (%)	38.6	35.5	21.5	22.1
ACR70 at 6 months (%)	11.4	13.1	4.7	3.2

Moreland LW et al. ACR Annual Meeting, October 2009, Abstract #1895.

TEAR: mean DAS28 στις 102 Εβδομάδες



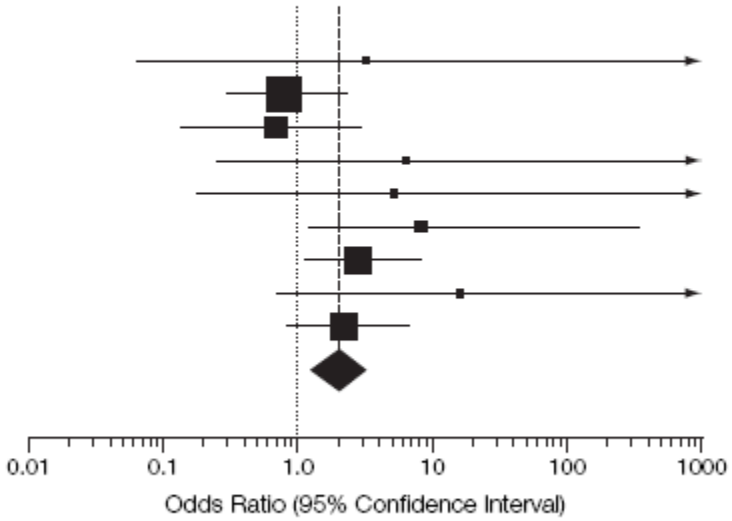
Moreland LW et al. ACR Annual Meeting, October 2009, Abstract #1895.

Αυξάνει ο κίνδυνος Λοιμώξεων με τη χορήγηση των αντι-TNFα παραγόντων?

- **All published RCTs with infliximab and adalimumab**
- **N = 9 (6 excluded, <12 weeks or differential exclusion criteria or lack of control group)**

Figure 3. Effect of Anti-TNF Antibody Therapy vs Control Therapy on Occurrence of 1 or More Serious Infections in Patients With Rheumatoid Arthritis

Source	Serious Infections, No./Total: Anti-TNF	Serious Infections, No./Total: Placebo	Odds Ratio (95% Confidence Interval)
Maini et al,[32] 1998	2/87	0/14	3.13 (0.06-Infinity)
Lipsky et al,[9] 2000	21/342	7/86	0.76 (0.30-2.18)
Furst et al,[8] 2003	4/318	6/318	0.66 (0.14-2.83)
Van de Putte et al,[10] 2003	4/214	0/70	6.33 (0.30-Infinity)
Weinblatt et al,[11] 2003	3/209	0/62	4.93 (0.19-Infinity)
Keystone et al,[6] 2004	16/419	1/200	7.90 (1.21-332.96)
St Clair et al,[7] 2004	40/749	6/291	2.68 (1.11-7.81)
Van de Putte et al,[33] 2004	11/434	0/110	15.34 (0.71-Infinity)
Westhovens et al,[34] 2004	25/721	6/361	2.13 (0.84-6.39)
Total	126/3493	26/1512	2.01 (1.31-3.09)
Test for overall effect: Mantel-Haenszel $\chi^2 = 9.1$; $P = .002$	3.6%	1.7%	



TNF indicates tumor necrosis factor. Size of the data markers is proportional to the statistical weight of the trial.

- 126 σοβαρές λοιμώξεις σε ΡΑ υπό infliximab ή adalimumab
- 12 ήσαν κοκκιωματώδεις, οι υπόλοιπες βακτηριακές
- OR για τις σοβαρές λοιμώξεις: 2.0 (95% CI 1.3- 3.1)

Bongartz T et al, JAMA 2006;295:2275-85

Κίνδυνος σοβαρών βακτηριακών λοιμώξεων

Ο κίνδυνος για νοσηλεία ήταν ~2-φορές υψηλότερος γενικά (σε περίοδο 20 μηνών) και

4-φορές υψηλότερος τους πρώτους 6 μήνες σε σύγκριση με αυτούς που λάμβαναν μόνο MTX (ηλικία, ΧΑΠ, ΣΔ)

Table 2. Types of physician-confirmed "definite" bacterial infections during hospitalization*

	TNFα antagonist patients	MTX-only patients
No. (%) of patients with any infection	65 (2.7)	58 (2.0)
Site-specific infections, no.		
Pneumonia/empyema	25	23
Cellulitis/soft tissue	23	17
Bacteremia/sepsis	7	8
Kidney/urinary tract	8	10
Postoperative	7	5
Device-associated	6	4
Septic arthritis	4	4
Gastroenteritis	1	5
Abdominal abscess	1	2
Osteomyelitis	1	3
Bacterial sinusitis	3	0
Diverticulitis	0	1
Total†	86	82

Curtis JR et al, Arthritis Rheum 2007;56:1125-33

H. Zoster infection with TNF inhibitor Use

- RABBIT (German Biologics Registry) 2001-06
- DMARD vs TNF (5040) pts (ETN, ADA, INF)
  - 86 Varicella-Zoster Viral (VZV) infections in 82 patients
    - **TNF use "may" increase risk of H. Zoster**
    - 12 hospitalized
    - 4 H. zoster ophthalmicus
- VZV Rates: TNF vs DMARD
- Significantly Increased Risk w
  - Age (1.73),
  - ↑DAS (1.36),
  - Pred ≥10mg (2.9)

		95%CI
ETN	1.36	(0.73-2.5)
MAbs	1.82	(1.05-3.15)
All TNF	1.63	(0.97-2.4)

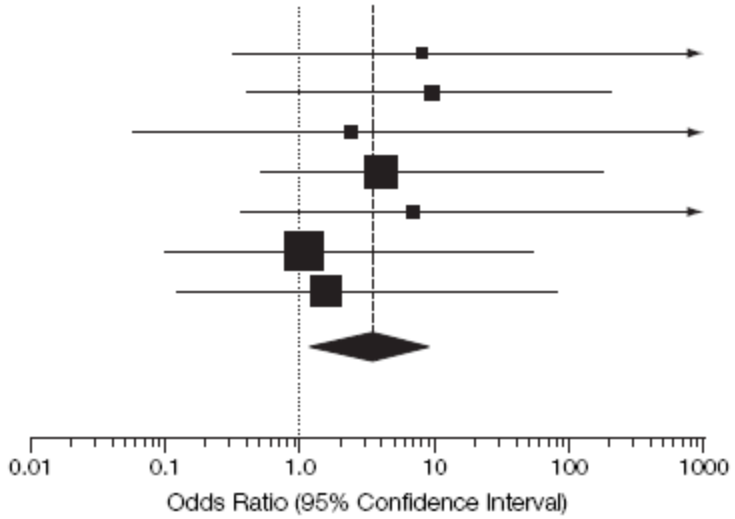
Strangfeld A, et al. JAMA 2009; 301:737

Αυξάνει ο κίνδυνος νεοπλασιών με τη χορήγηση των αντι-TNFα παραγόντων?

Figure 2. Effect of Anti-TNF Antibody Therapy vs Control Therapy on Occurrence of 1 or More Malignancies in Patients With Rheumatoid Arthritis

Source	Malignancies, No./Total: Anti-TNF	Malignancies, No./Total: Placebo	Odds Ratio (95% Confidence Interval)
Lipsky et al,[9] 2000	5/342	0/86	7.57 (0.30-Infinity)
Furst et al,[8] 2003	4/318	0/318	9.11 (0.40-199.49)
Weinblatt et al,[11] 2003	1/209	0/62	2.29 (0.06-Infinity)
Keystone et al,[6] 2004	8/419	1/200	3.87 (0.51-172.73)
St Clair et al,[7] 2004	4/749	0/291	6.58 (0.36-Infinity)
Van de Putte et al,[33] 2004	4/434	1/110	1.01 (0.10-50.39)
Westhovens et al,[34] 2004	3/721	1/361	1.50 (0.12-79.18)
Total	29/3192	3/1428	3.29 (1.19-9.08)

Test for overall effect:
Mantel-Haenszel $\chi^2 = 5.2$; $P = .02$



TNF indicates tumor necrosis factor. Size of the data markers is proportional to the statistical weight of the trial.

OR για νεοπλασίες: 3.3 (95% CI 1.2- 9.1)

Bongartz T et al, JAMA 2006;295:2275-85

Medication costs

Drug	Approximate time to benefit	Usual maintenance dose	Annual drug cost (cost of generics), dollars*
Hydroxychloroquine	2–6 months	200 mg twice a day	1,056 (559)
Sulfasalazine	1–3 months	1,000 mg 2–3 times a day	509–763 (205–308)
Methotrexate	1–2 months	Oral 7.5–20 mg/week; injectable 7.5–20 mg/week	697–1,859 (259–691); 419–806 (42–81)
Leflunomide	4–12 weeks (skewed earlier)	20 mg/day in a single dose, if tolerated; otherwise, 10 mg/day†	2,938
Etanercept	A few days to 12 weeks	25 mg subcutaneously twice a week	15,436
Infliximab plus oral and subcutaneous methotrexate	A few days to 4 months	3–10 mg IV every 8 weeks or 3–5 mg IV every 4 weeks‡	13,940–30,287 or 28,040–36,694§
Azathioprine	2–3 months	50–150 mg/day	579–1,737 (471–1,414)
D-penicillamine	3–6 months	250–750 mg/day	865–2,595 (398–1,194)
Gold, oral	4–6 months	3 mg twice a day	1,622
Gold, intramuscular	3–6 months	25–50 mg intramuscularly every 2–4 weeks¶	198# (142)
Minocycline	1–3 months	100 mg twice a day	2,592 (582)
Cyclosporine	2–4 months	2.5–4 mg/kg/day**	4,432–8,859 (3,512–7,022)
Staphylococcal protein A immunoadsorption	3 months	Weekly for 12 weeks	20,433††

ACR Treatment Guidelines; Arthritis Rheum 2002; 46:328-346

Συνεπώς

- Έκβαση νόσου βελτιώνεται όταν υπάρχει καθορισμένος στόχος θεραπείας
- **Ύφεση ή χαμηλή δραστηριότητα νόσου**
- **Early treatment and "Tight control" of RA**
- Έναρξη με MTX (προοδευτική αύξηση δόσης)
- Συνδυασμός DMARDs
- **Αποτελεσματικότητα, Ασφάλεια, Κόστος, Προτίμηση ασθενούς**