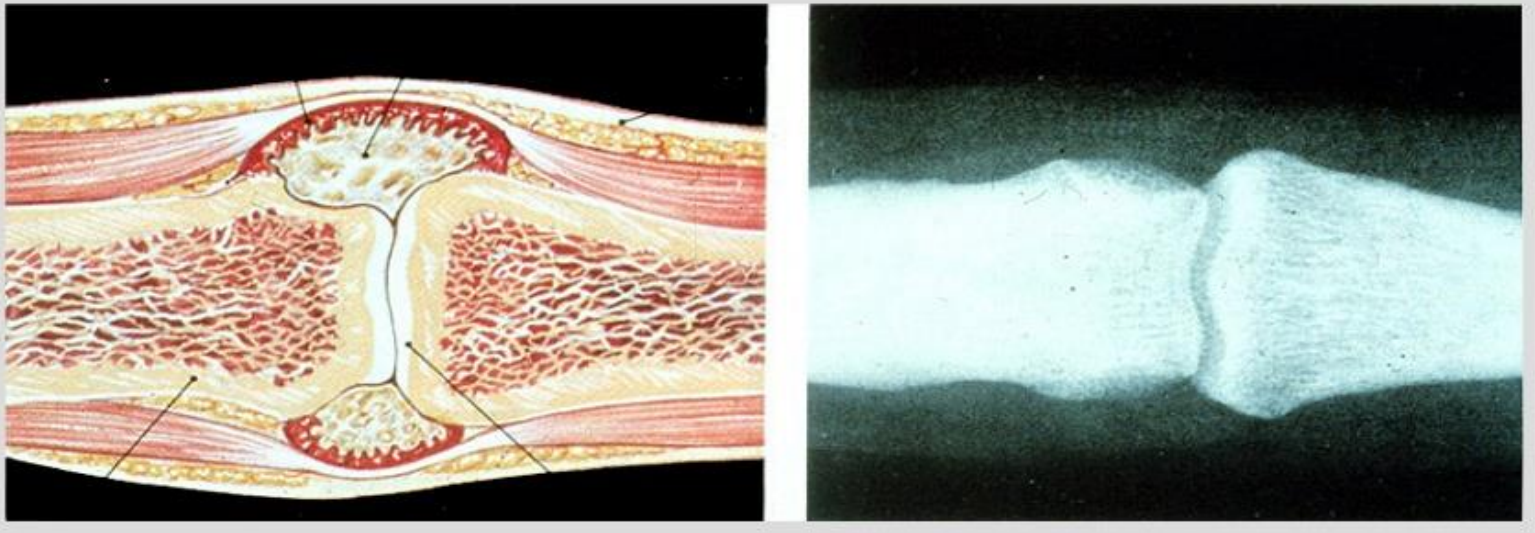
Οδικός χάρτης στη θεραπευτική της ΡΑ

Αλέξανδρος Α. Δρόσος

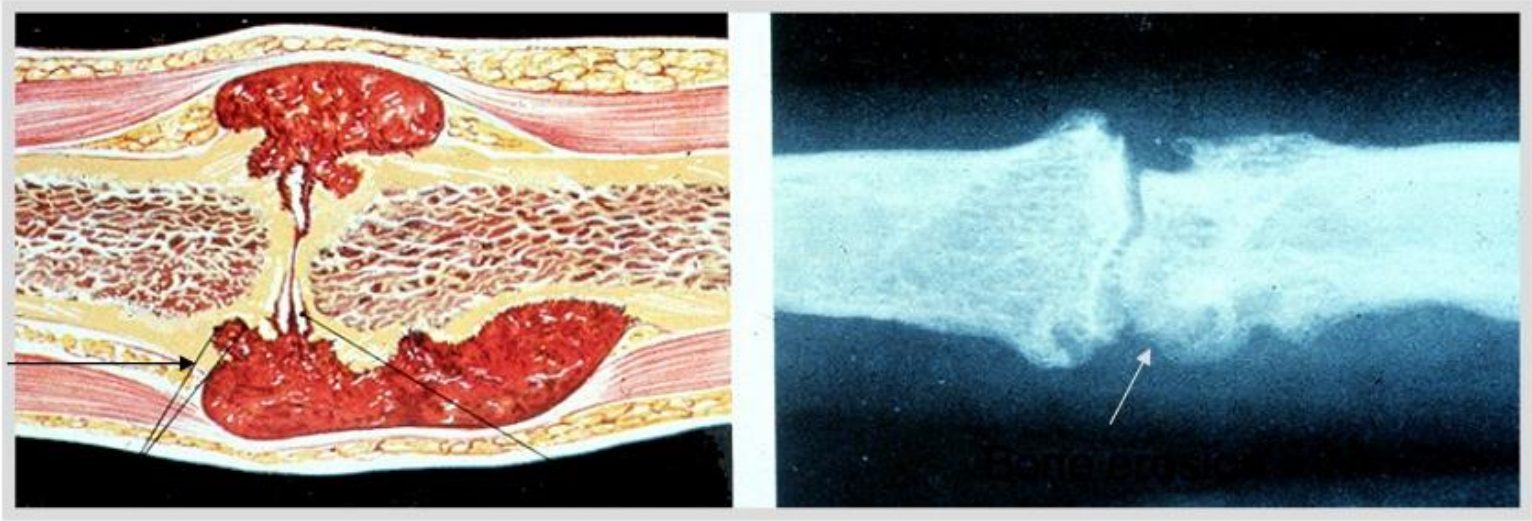
Ιατρική Σχολή Πανεπιστημίου Ιωαννίνων

Rheumatoid arthritis: progressive joint destruction & disability

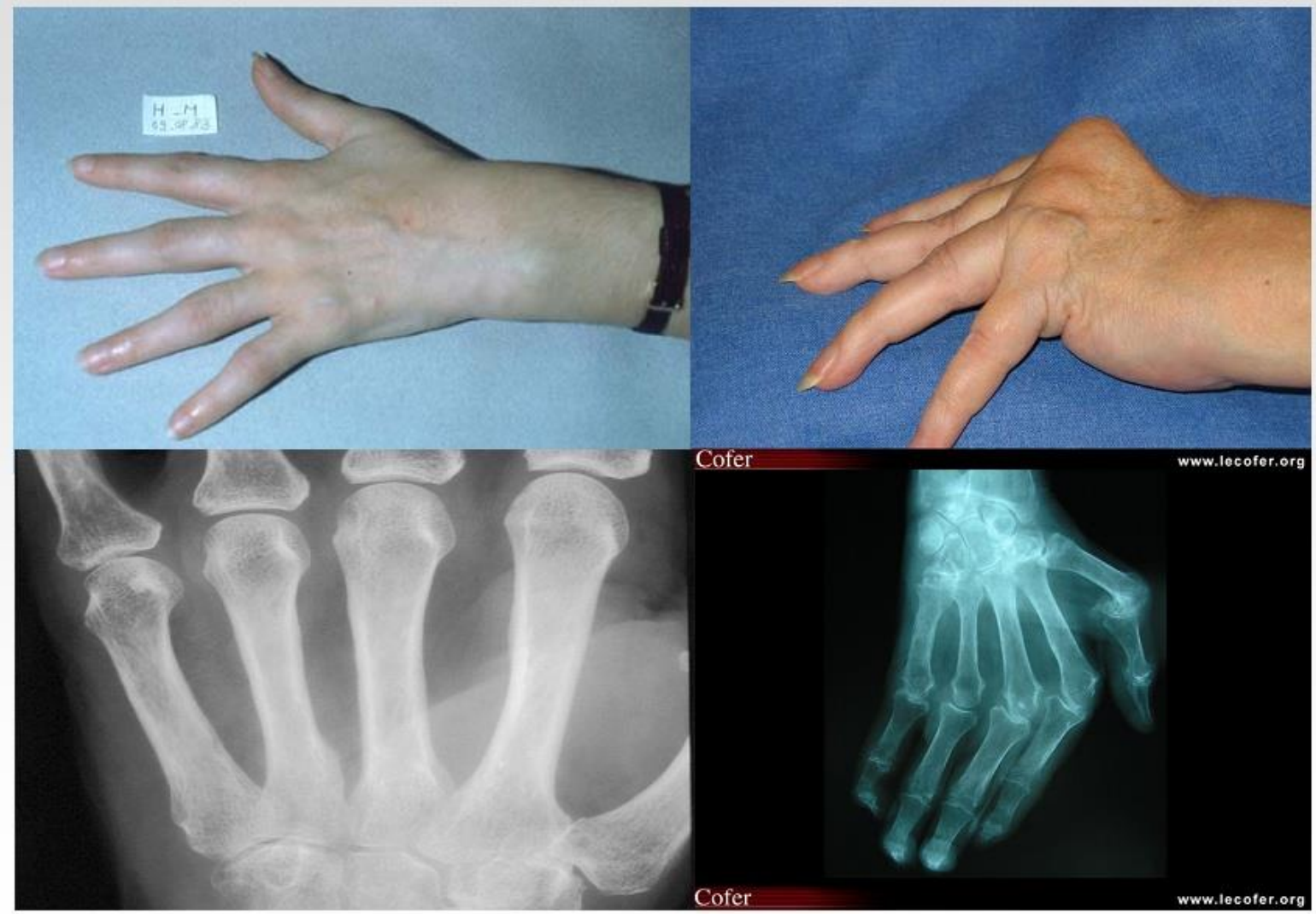
Normal

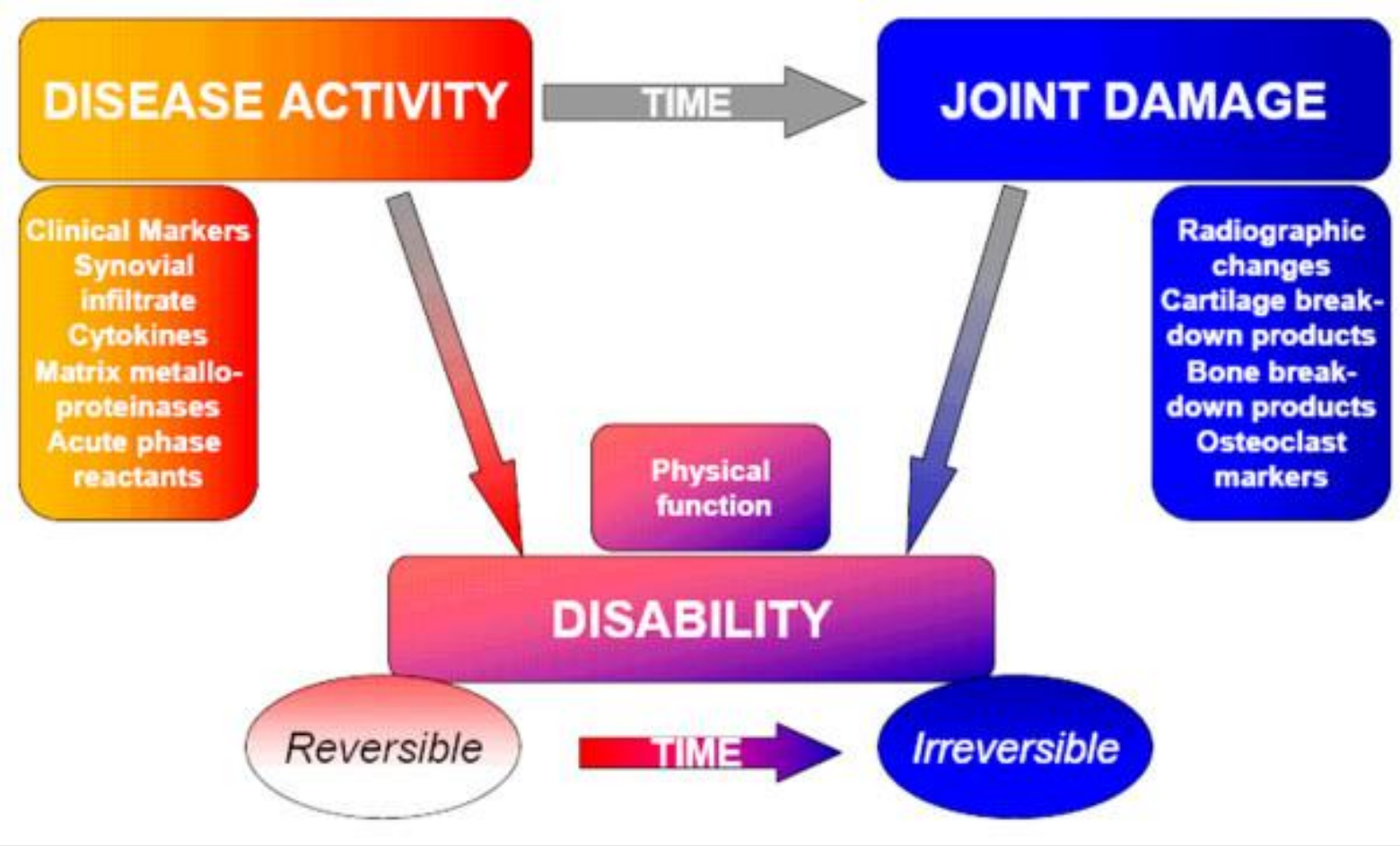


RA pannus



Early vs established RA





Smolen JS et al. Arthritis Res Ther 2008;10:208.

Strategy of RA treatment

- Inflammation is bad and causes structural damage and disability
- Structural damage occurs early
- Inflammation + time deteriorate structural damage and disability
- Inflammation is treatable
- Thus early and aggressive treatment is required

Case 1

- 33 year old female previously healthy, no medications
- Right 2nd MCP pain and swelling x 5 weeks
- AM stiffness 45 minutes
- O/E: swollen right 2nd & 3rd MCPs, right 5th MTP tender
- Rheumatoid factor + 42; CRP elevated 11
- Radiographs of hands and feet – no radiographic damage

Case 2

- 54 year old businessman
- PMHx: high cholesterol, no medications
- 10 week history of diffuse joint pain & swelling (shoulders, elbows, hands, knees, feet)
- AM stiffness – 4 hours
- On exam, 35 active joints, 22 effused joints
- Rheumatoid factor negative, CCP negative, CRP elevated
- X-Rays: osteopenia, periarticular osteoporosis, early erosive changes in the carpal bones

Which patient has worse prognosis?

A. Case 1

- 33 year old female previously healthy, no medications
- Right 2nd MCP pain and swelling x 5 weeks
- AM stiffness 45 minutes
- 2 swollen joints right hand
- Rheumatoid factor + 42; CRP 11;
- no radiographic damage

B. Case 2

- 54 year old businessman
- 10 week history of joint pain & swelling (shoulders, elbows, hands, knees, feet)
- AM stiffness – 4 hours
- 35 active joints, 22 effused joints
- Rheumatoid factor negative
- X-Rays: osteopenia, periarticular osteoporosis, early erosive changes in the carpal bones

Case 3

- GP refer patient to rheumatologist (you) with the following information:
  - Female 40 years old, previous good health. Employed secretary
  - Swollen joints in hands and feet for 3 months
  - ESR 40 mm/h, CRP 50 mg/l
  - RF 60 IU/l, Anti CCP 80 IU/l
  - No radiographic examination, Starts treatment with NSAIDs
- Which priority on your waiting list?

Which priority on your waiting list?

- Regular waiting list – at least 3 months
- Examined within 3 months
- Examined within a month
- Radiographs / MRI within a week and examined clinically within 3 weeks
- Hand and wrist radiographs and immediate appointment for clinical evaluation

Case 3

- You receive the patient after 2 weeks and do the following findings
  - 10 out of 28 swollen joints
  - MTP also swollen
  - DAS28 6.0
- You would start with DMARD or anti TNF-which?
- Would you also start prednisolone?

You would start with DMARD or anti TNF - which?

- Start MTX + folic acid
- Start either sulphasalazine and/or antimalarials
- Start MTX + folic acid + sulfasalazine + antimalarials
- Start MTX + anti TNF agent

Would you also start prednisolone?

- Yes
- No

Corticosteroids

- Systemic use
- Intraarticular use

Case 3

- MTX was chosen. Would any of the following factors have influenced your decision:
  - Male instead of female
  - Younger age
  - Higher APR
  - Higher antiCCP concentration
  - Radiographic erosions
  - Bone marrow edema MRI
  - Anti-nuclear antibodies
  - Enthesitis
- What would be your treatment target?
- When (after how many weeks if not reaching the target) would you consider “add on” with anti-TNF?

Diagnosis of RA: ACR criteria

At least four of the following criteria

- Morning stiffness >1 hour
- Arthritis of ≥3 joint areas
- Arthritis of hand joints
- Symmetric arthritis
- Rheumatoid nodules
- Serum rheumatoid factor
- **Radiographic changes**

Must be present for at least 6 weeks

Arnett FC et al. Arthritis Rheum 1988;31:315–24

New criteria for RA diagnosis

Patients are definitively diagnosed with RA if they score 6 or more points according to the following criteria:

Joint involvement

1 medium-large joint **(0 points)**

2-10 medium-large **(1 point)**

1-3 small joints **(2 points)**

4-10 small joints **(3 points)**

More than 10 small joints **(5 points)**

Serology

Not positive for either rheumatoid factor or anti-citrullinated protein antibody **(0 points)**

At least one of these two tests are positive at low titer, defined as more than the upper limit of normal but not higher than three times the upper limit of normal **(2 points)**

At least one test is positive at high titer, defined as more than three times the upper limit of normal **(3 points)**

Duration of synovitis

Lasting fewer than 6 weeks **(0 points)**

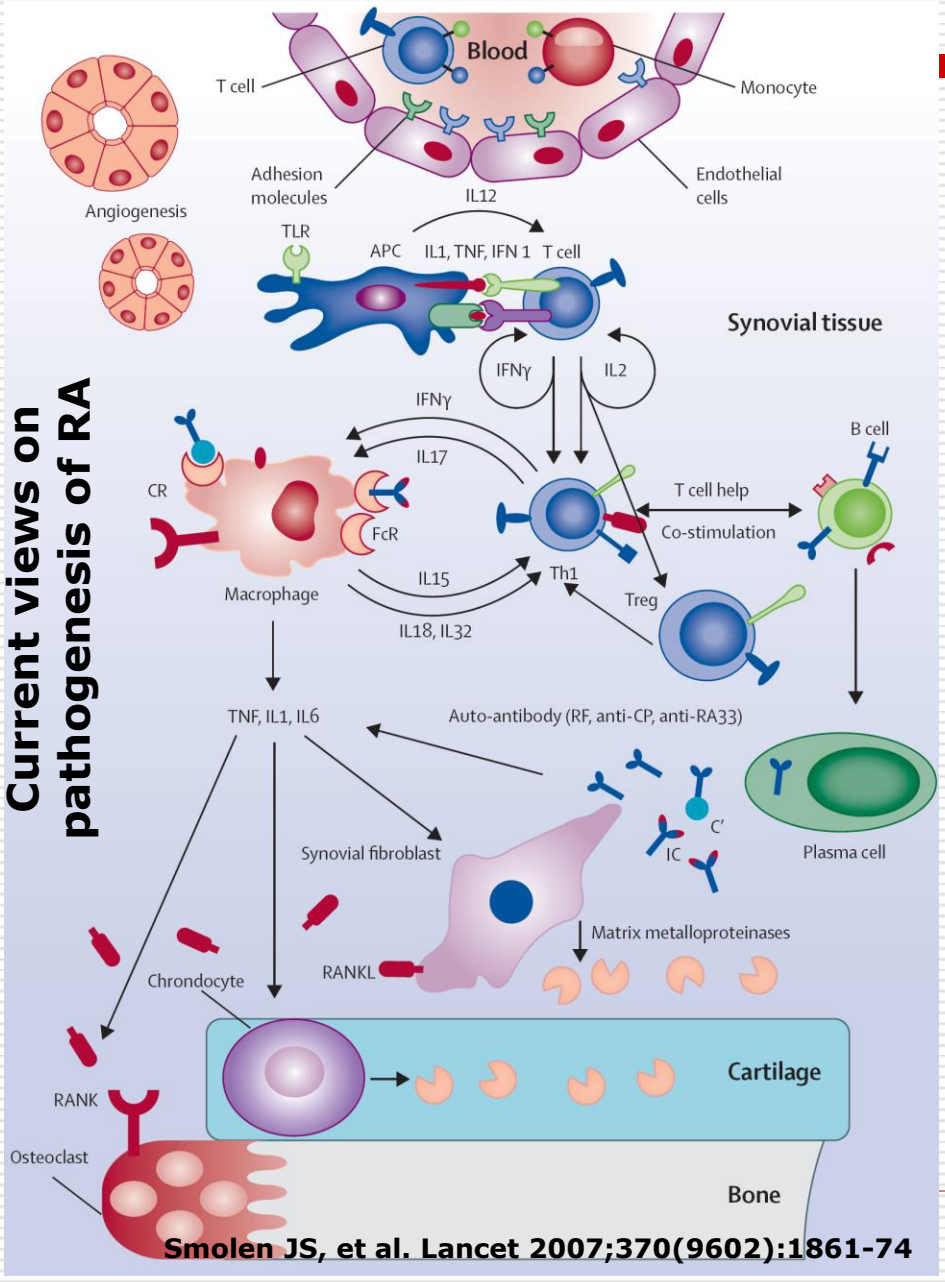
Lasting 6 weeks or longer **(1 point)**

Acute-phase reactants

Neither C-reactive protein nor erythrocyte sedimentation rate is abnormal **(0 points)**

Abnormal CRP or abnormal ESR **(1 point)**

What have we learned during these years?



- Better understanding of pathophysiology
- The role of cytokines
- The role of T and B-cells
- Prognostic factors
- Disease activity, monitoring and treat to target
- Early treatment

Markatseli TE, Papagoras C, Drosos AA

Prognostic factors for erosive rheumatoid arthritis

Clin Exp Rheumatol 2010;28:114-23

Table I. Potential prognostic factors of radiological damage in rheumatoid arthritis.

Demographic	Genetic
- Age	- Shared epitope
- Sex	- PTPN22 gene
- Disease duration	Autoantibodies
- Smoking	- Rheumatoid factor
- Body mass index	- Anti-cyclic citrullinated peptide antibodies
Clinical	- Anti-peptidyl-arginine deiminase-4 antibodies
- Symmetrical polyarthritis	Bone markers
- Disease activity score	- Matrix metalloproteinase-3
- Health assessment questionnaire score	- RANKL/OPG ratio
- Extra-articular manifestations	- Human cartilage glycoprotein-39
Inflammatory markers	- Cartilage oligomeric matrix protein
- Erythrocyte sedimentation rate	- Collagen cross-linked C-telopeptide
- C-reactive protein	Early imaging damage

Markatseli TE, et al. Clin Exp Rheumatol 2010;28:114-23

Treat to target and systemic monitoring

- The hypertension or diabetes mellitus paradigm

Diabetes mellitus

- Normal glucose and decrease glucosylate hemoglobin (less than 6.3)
- LDL less than 90 mg/dl
- Blood pressure less than 120/80 mmHg

Atar D, Birkeland KA and Uhlig T

'Treat to target': moving targets from hypertension, hyperlipidaemia and diabetes to rheumatoid arthritis

Ann Rheum Dis 2010;69:629-30

Smolen JS, Aletaha D, Bijlsma JWJ, et al; for the T2T Expert Committee

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

Ann Rheum Dis 2010;69:631-37

Conclusion

The 10 recommendations are supposed to inform patients, rheumatologists and other stakeholders about strategies to reach optimal outcomes of RA based on evidence and expert opinion

Box 1 Recommendations

Overarching principles

(A) The treatment of rheumatoid arthritis must be based on a shared decision between patient and rheumatologist.

(B) The primary goal of treating the patient with rheumatoid arthritis is to maximise long-term health-related quality of life through control

of symptoms, prevention of structural damage, normalisation of function and social participation.

(C) Abrogation of inflammation is the most important way to achieve these goals.

(D) Treatment to target by measuring disease activity and adjusting therapy accordingly optimises outcomes in rheumatoid arthritis.

Smolen JS, et al. Ann Rheum Dis 2010;69:631-37

Recommendations

(1) The primary target for treatment of rheumatoid arthritis should be a state of **clinical remission**.

(2) Clinical remission is defined as the **absence** of signs and symptoms **of significant inflammatory disease activity**.

(3) While remission should be a clear target, based on available evidence **low disease activity** may be an acceptable alternative therapeutic goal, particularly in established long-standing disease.

(4) Until the desired treatment target is reached, drug therapy should be adjusted at least **every 3 months**.

(5) Measures of disease activity must be obtained and documented regularly, as frequently as **monthly** for patients with high/moderate disease activity or less frequently (such as **every 3–6 months**) for patients in sustained low disease activity or remission.

(6) The use of validated **composite measures of disease activity**, which include joint assessments, is needed in routine clinical practice to guide treatment decisions.

(7) Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity.

(8) The desired treatment target should be maintained throughout the remaining course of the disease.

(9) The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of **co-morbidities**, patient factors and **drug-related risks**.

(10) The patient has to be appropriately **informed about the treatment target** and the strategy planned to reach this target under the supervision of the rheumatologist.

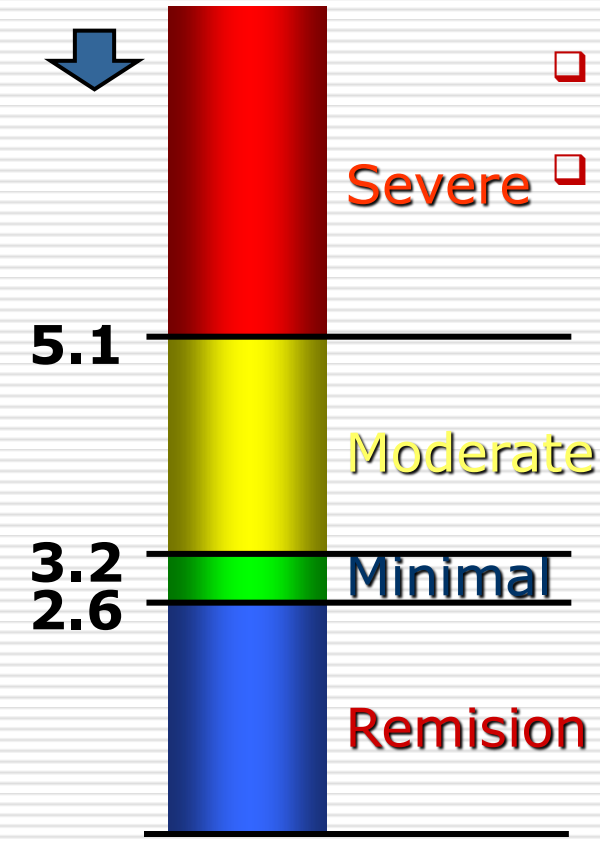
Smolen JS, et al. Ann Rheum Dis 2010;69:631-37

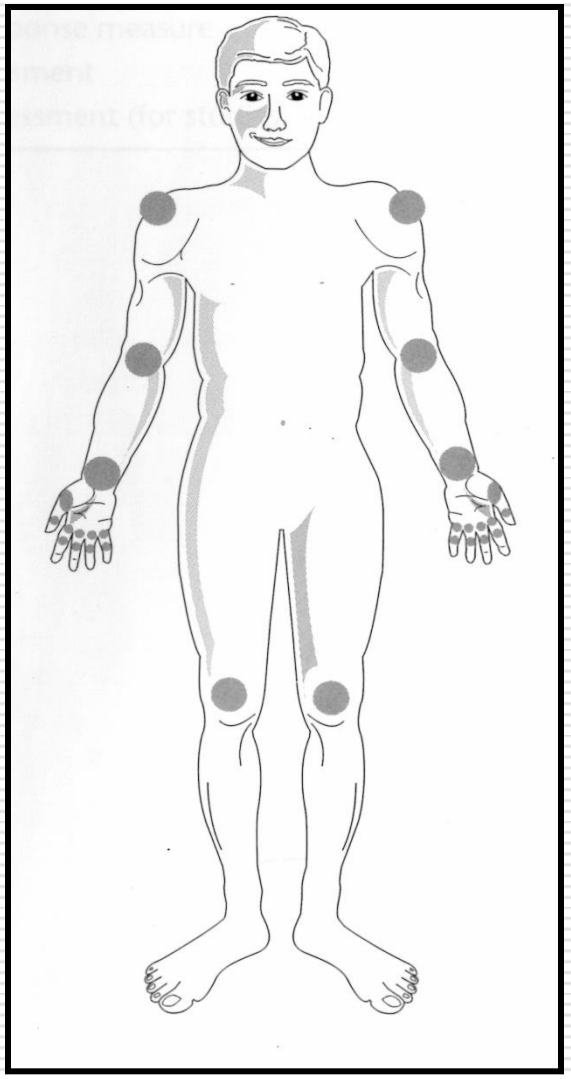
Remission is Complex

- Clinical Remission: ACR/DAS criteria, or normal acute phase response, no clinical synovitis
- Imaging Remission: no significant synovitis on sensitive imaging
- True Remission: a state of no detectable disease with no progression of structural damage

DAS28: disease activity

- Number of tender joints
- Number of swollen joints
- ESR (mm/h)
- General health (VAS)





DAS 28 (4 variables)=0.56*TE28+0.28*SW28+0.7*ESR+0.014*GH

Smith N, Ding T, Butt S, Gadsby K and Deighton C

The importance of the baseline Disease Activity Score 28 in determining responders and non-responders to anti-TNF in UK clinical practice

Rheumatology 2008;47:1389–1391

Katchamart W, Bombardier C

Systematic monitoring of disease activity using an outcome measure improves outcomes in rheumatoid arthritis

J Rheumatol 2010 May 1 [Epub ahead of print]

Conclusion

Systematic monitoring of disease activity, aiming for at least low disease activity, and frequent followup improves outcome in RA

Targets of therapy in RA

Clinical remission
DAS-28 <2,6

↓

Maintenance of quality of live

↓

Inhibition of structural damage

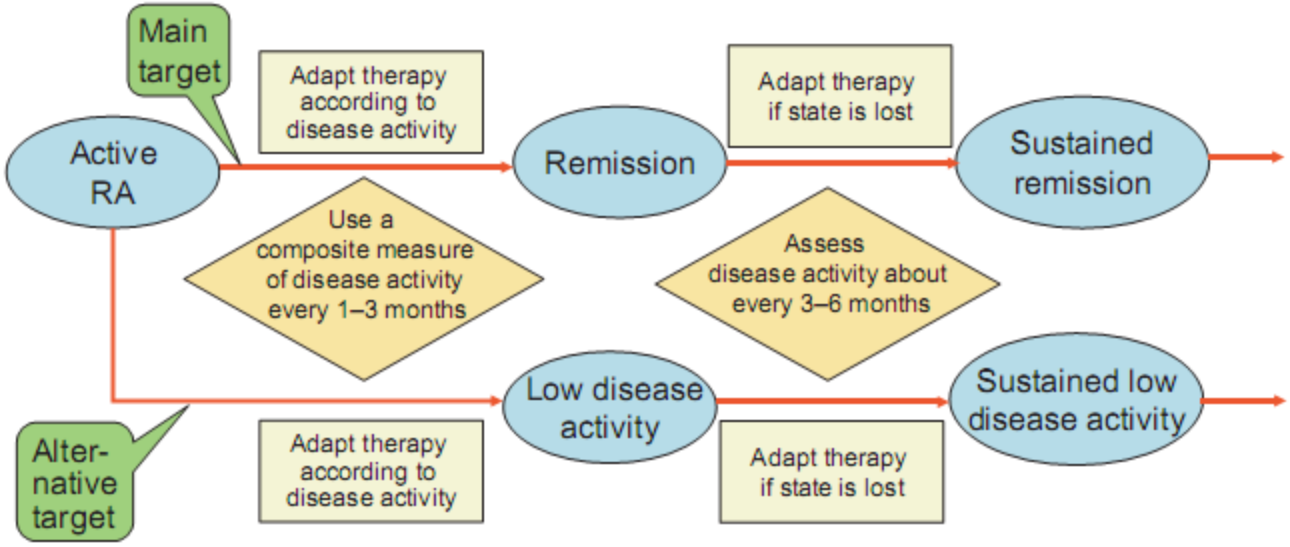
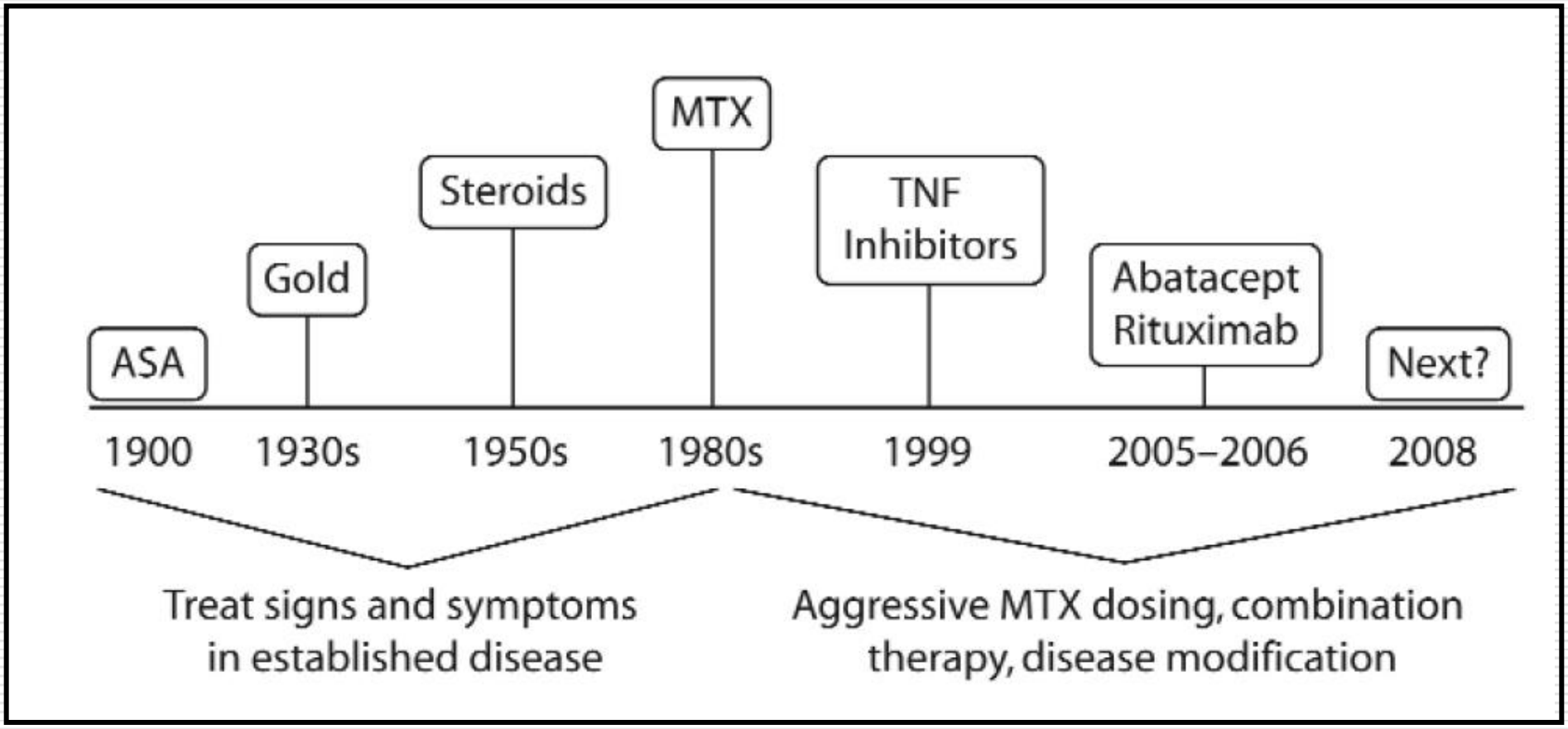


Figure 1 Algorithm for treating rheumatoid arthritis (RA) to target based on the recommendations provided in box 1 and discussed in more detail in the explanatory notes. Indicated as separate threads are the main target (remission and sustained remission) and the alternative target (low disease activity in patients with long-term disease), but the approaches to attain the targets and sustain them are essentially identical. Adaptation of therapy should usually be done by performing control examinations with appropriate frequency and using composite disease activity measures which comprise joint counts.

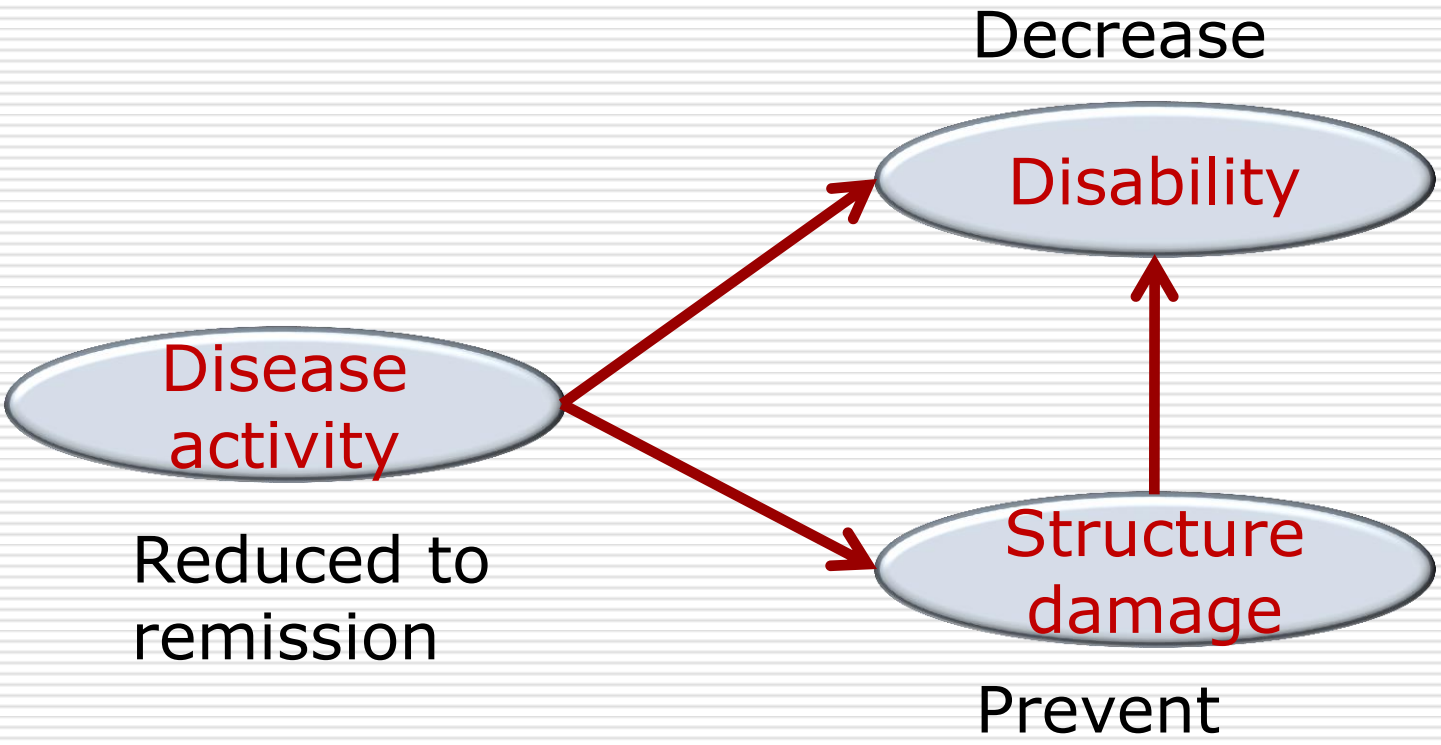
Smolen JS, et al. Ann Rheum Dis 2010;69:631-37

RA medication timeline

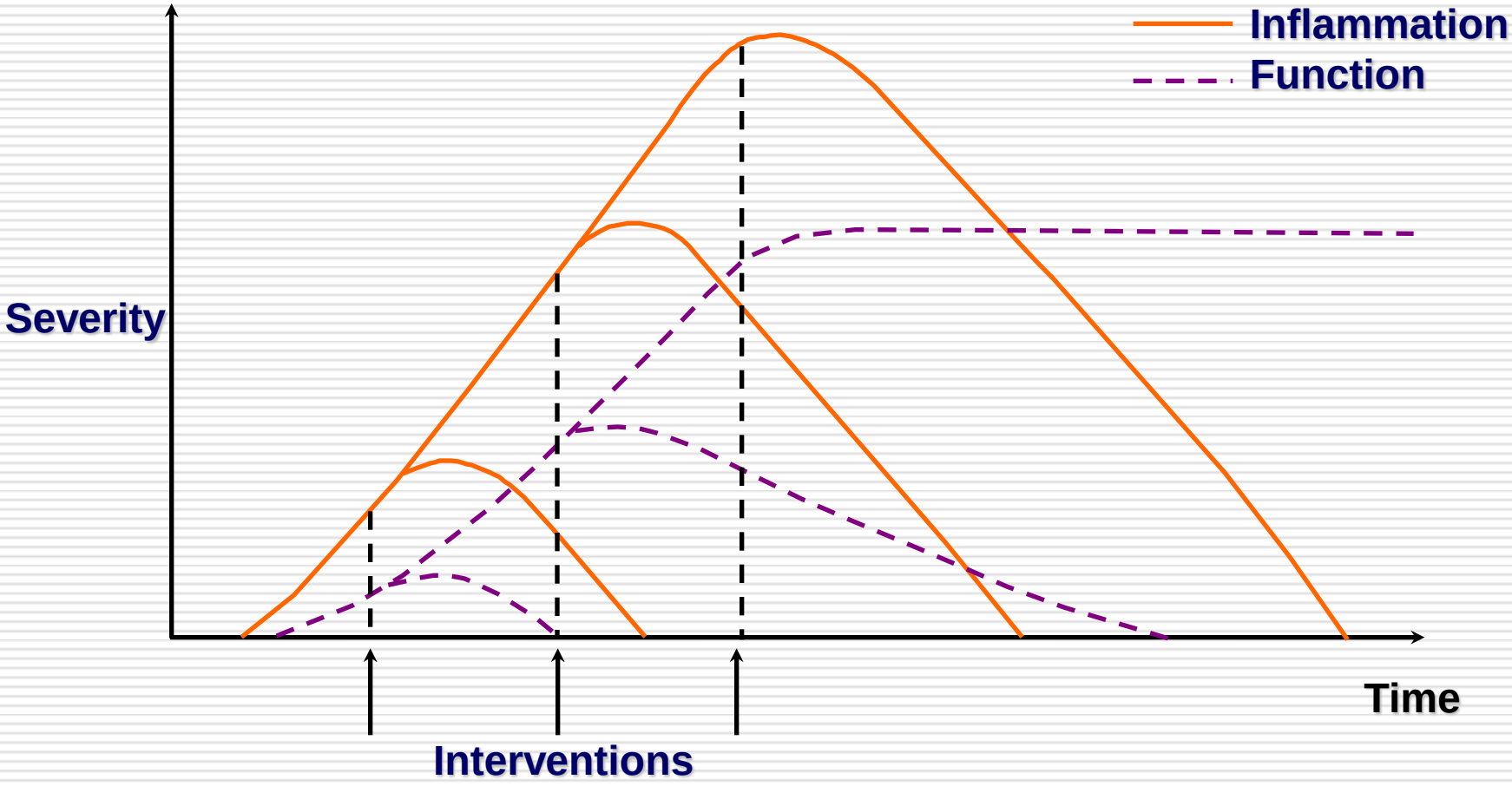


Cohen SB, et al. J Rheumatol 2008;35 (suppl 81):4-30

Objective of RA treatment



Effect of RA Disease Duration on Inflammation and Function

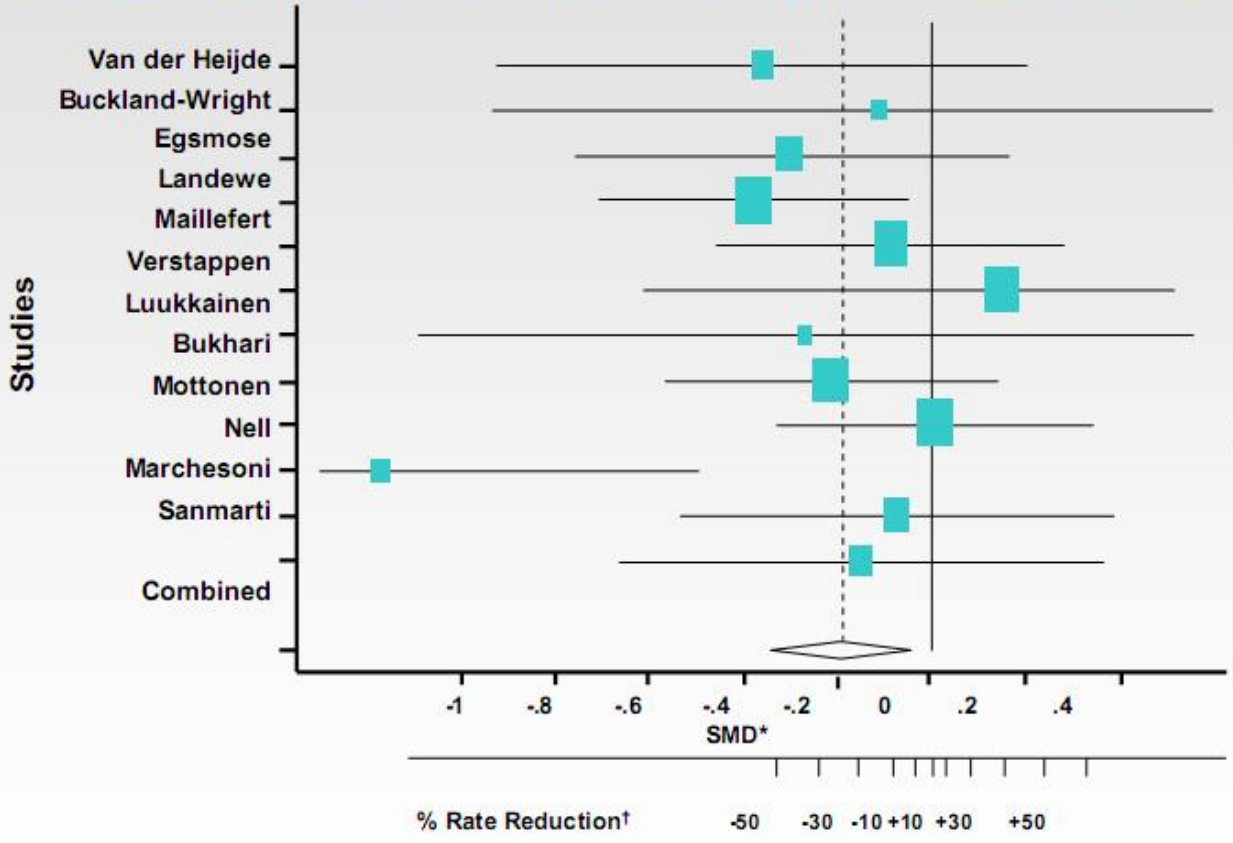


Emery P. Ann Rheum Dis. 1995;54:944

Early DMARD initiation alters radiographic progression rate

Meta-analysis of 12 studies comparing early vs late initiation:

Average delay in treatment start: 9 months; median follow-up: 3 years



Reduction in progression rate: 1.4 Sharp units/year (33% reduction)

n=1133

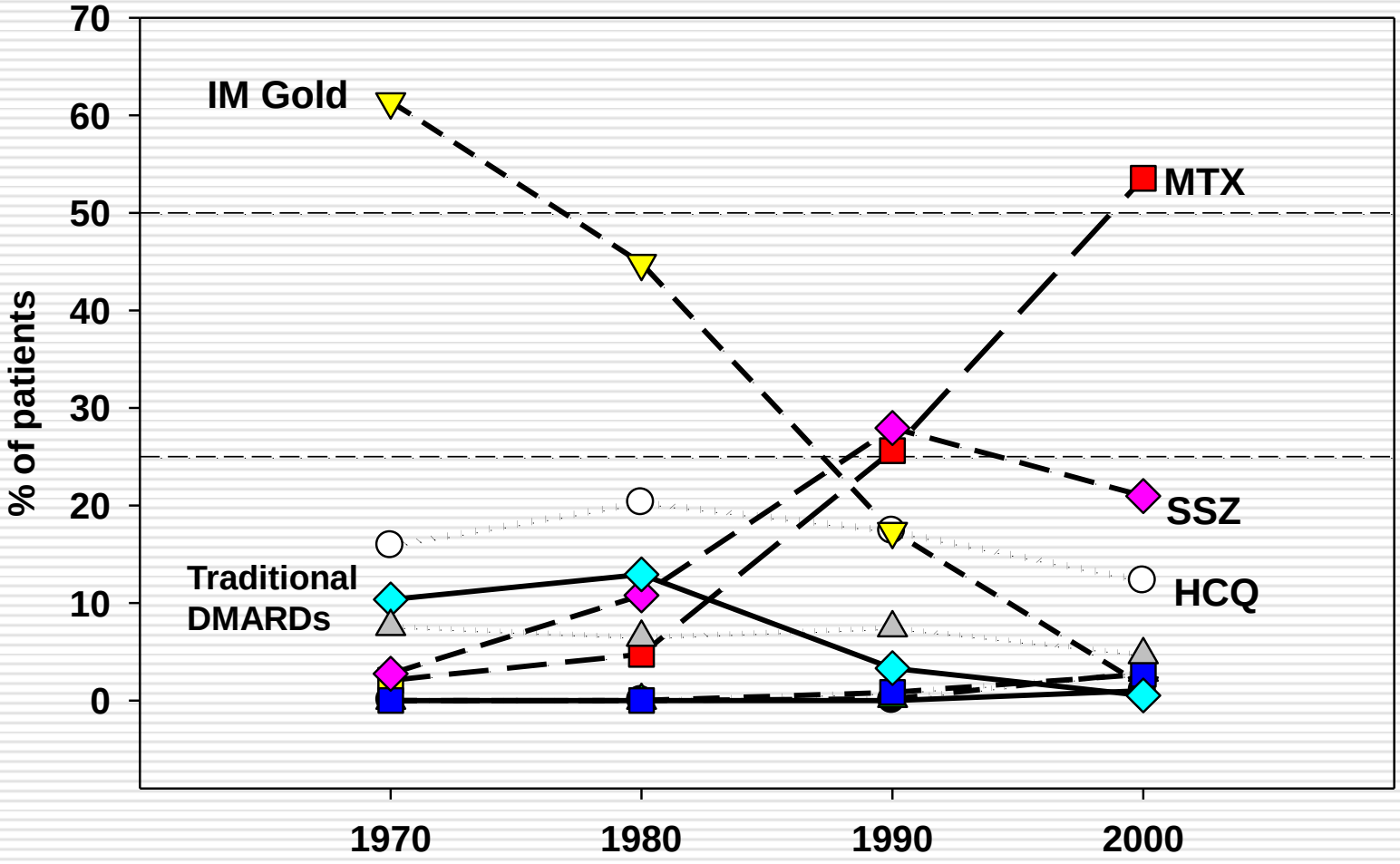
More progressive disease benefitted more from earlier treatment (*P*=0.04)

Finckh A, et al. Arthritis Rheum 2006;55:864-872

DMARDs used in RA patients

Drug	Mechanism of action	Approximate time to benefit	Rout of administration	Usual dose	Toxic effect
Methotrexate	Inhibits DNA purine synthesis, ↑ adenosine-medicated anti-inflammatory effects	1-2 months	pos or by injection	7.5-25 mg once weekly	Myelosuppression, hepatotoxicity, pulmonary fibrosis, nausea, oral ulcers, teratogenic effects
Leflunomide active metabolite A771726	Inhibits de novo pyrimidine synthesis	1-2 months	pos	Loading dose of 100 mg daily for 3 days, followed by 20 mg daily	Gastrointestinal tract, dysfunction, hepatotoxicity, teratogenic
Sulfasalizine	↑ extracellular adenosine ↓ activation of NFkB	2-3 months	pos	2-3 g/day in a twice daily dosing regimen	Gastrointestinal effects, myelosuppression, hepatotoxicity, skin rash
Cyclosporine A	Inhibits IL-2 production and proliferation of T-cells	1-2 months	pos	2.5-3.5 mg/kg per day	Nephrotoxicity, hypertension, hypertrichosis, tremor, gram hyperplasia
Hydroxychloroquine	↑ intracellular pH and interferes with antigen presentation	2-4 months	pos	200-400 mg/day	Retinal toxicity maculopathy, bull's eye

The initial DMARD in 1970's to 2000's in Europe; The raise of methotrexate



Gaujoux-Viala C, Smolen JS, Landewé R, et al

Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis

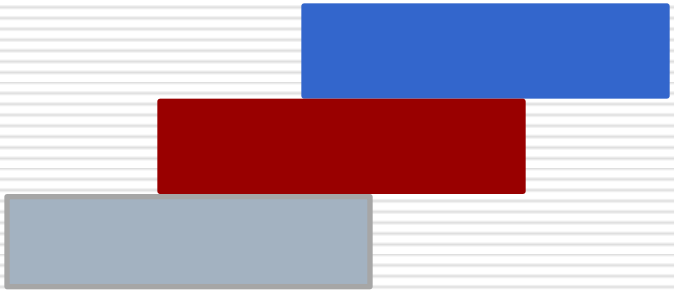
Ann Rheum Dis 2010;69:1004-9

Conclusion

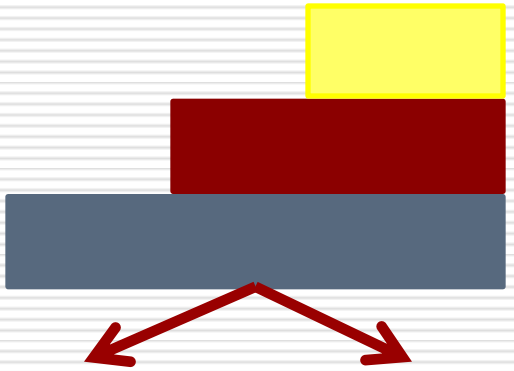
MTX was well-tolerated and effective in reducing signs and symptoms, disability and structural damage. A comparison with other synthetic DMARDs was in favour of MTX, though at the tested doses MTX and leflunomide were equally effective

Strategies of RA treatment

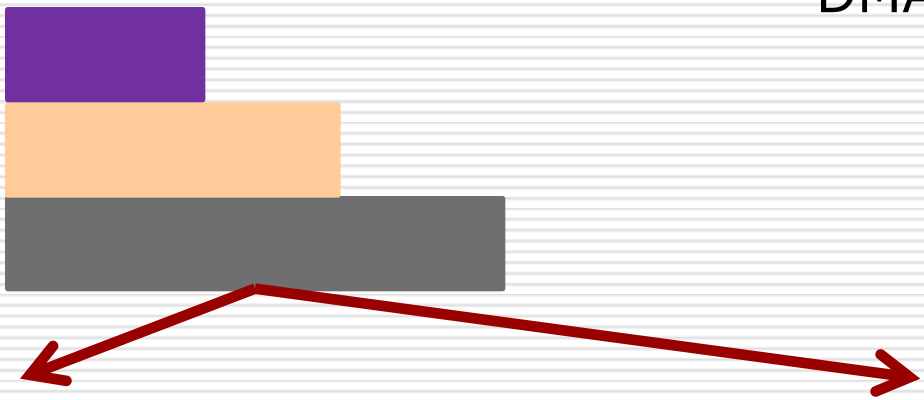
Sequential monotherapy



Step-up combination

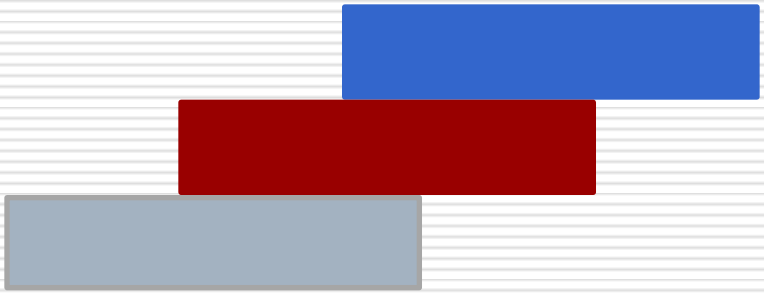


Initial combination



Strategies of RA treatment

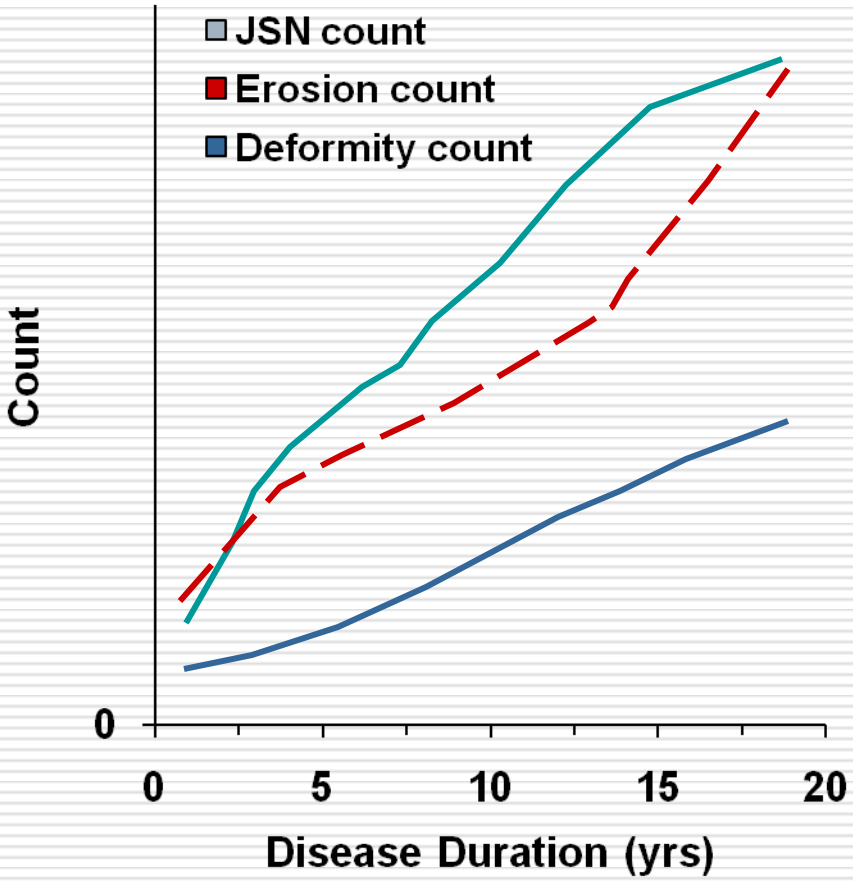
Sequential monotherapy



Is sequential monotherapy doing enough?

Radiographic Progression Despite DMARD Treatment

- Study of radiographic outcomes in early RA
  - 256 patients with early RA (<2 years); treated and followed long term for radiographic progression
  - Radiographic progression was evident despite treatment

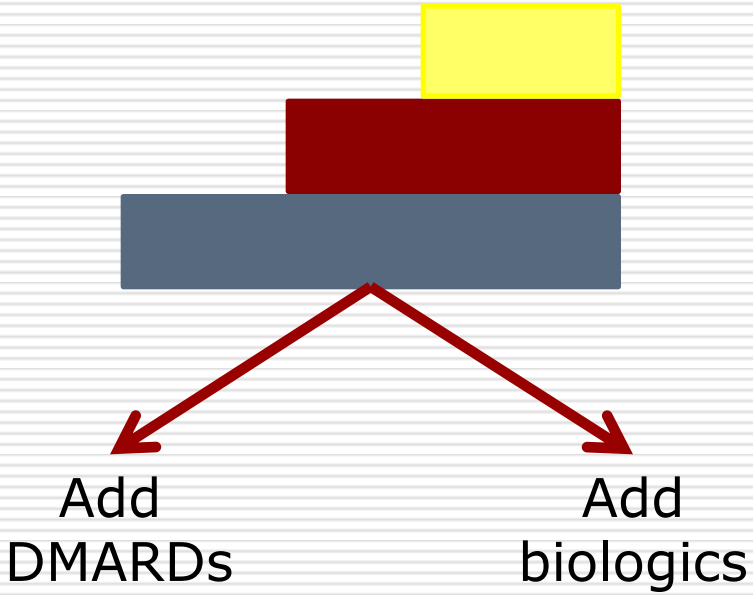


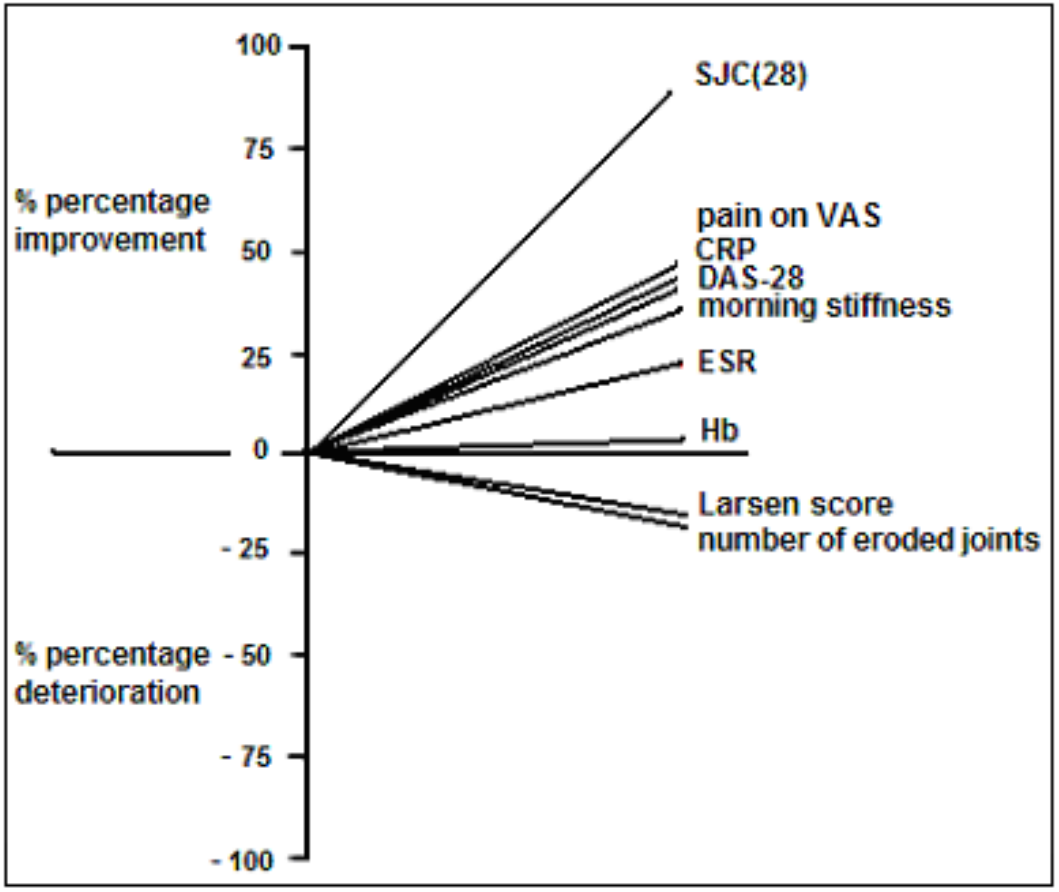
JSN = Joint space narrowing

Wolfe F and Sharp JT. Arthritis Rheum. 1998;41(9):1571-1582.

Strategies of RA treatment

Step-up combination





Dissociation between clinical and radiological outcome. Improvement is the mean actual change during the 10-year period expressed as a percentage of the value at enrolment. Deterioration is the mean actual change expressed as a percentage of the total change possible

van Vollenhoven RF, Ernestam S, Geborek P, et al

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

Lancet 2009;374(9688):459-66

INTERPRETATION

In patients with early rheumatoid arthritis in whom methotrexate treatment failed, **addition of a tumour necrosis factor antagonist to methotrexate monotherapy is clinically superior** to addition of conventional disease-modifying antirheumatic drugs

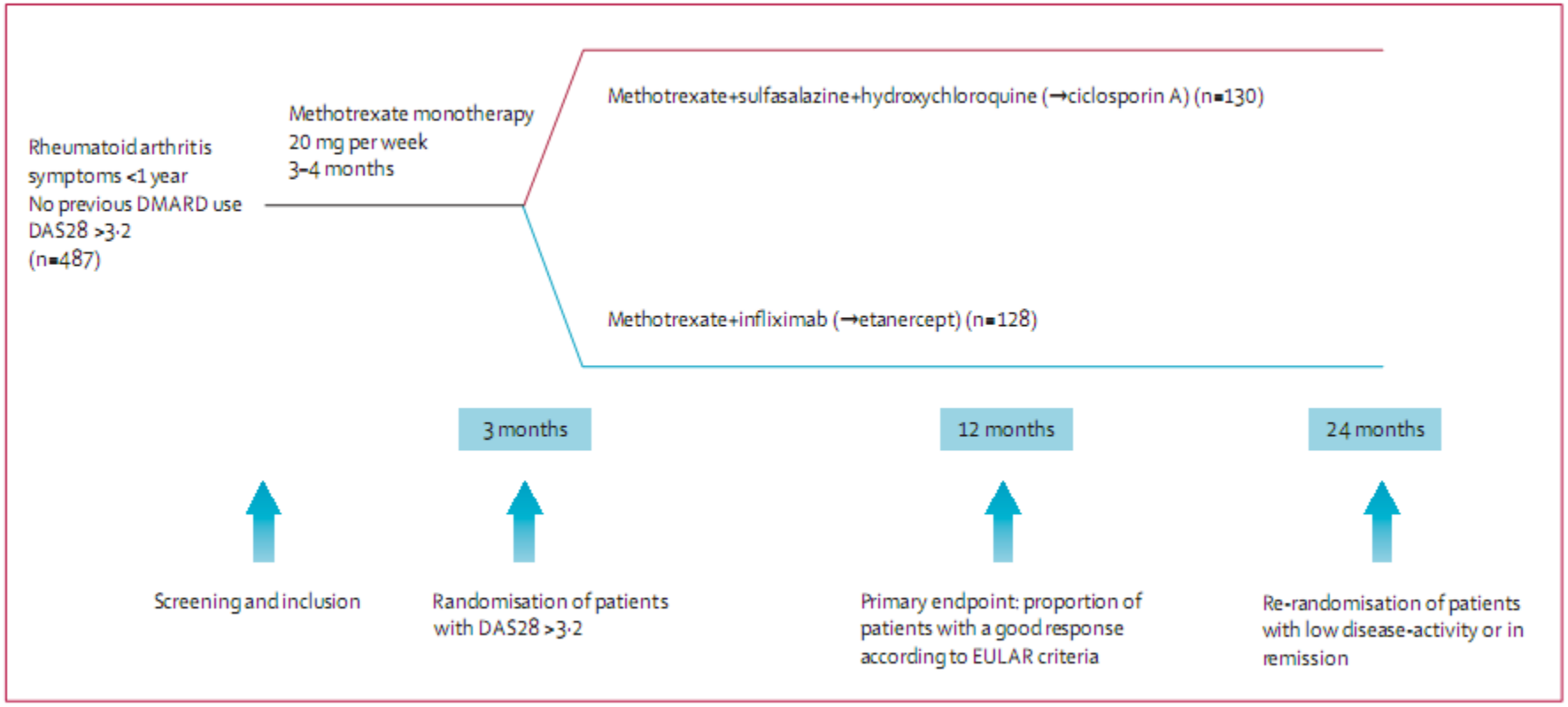


Figure 1: Schematic of the Swefot trial

van Vollenhoven RF, et al. Lancet 2009;374(9688):459-66

	Sulfasalazine and hydroxychloroquine (n=130)	Infliximab (n=128)
Age (years)	52·9 (13·9)	51·1 (13·3)
Women	101 (78%)	97 (76%)
Symptom duration (months)	6·3 (3·6)	6·2 (3·5)
Rheumatoid factor-positive	85 (65%)	88 (69%)
DAS28 score at baseline	5·98 (0·96)	5·91 (0·93)
Health assessment questionnaire score at baseline	1·32 (0·60)	1·27 (0·60)
DAS28 score at randomisation	4·79 (1·05)	4·91 (0·98)
Taking low-dose glucocorticoids at baseline	10 (8%)	8 (6%)

Data are mean (SD) or number of patients (%).

Table 1: Characteristics of randomised population

van Vollenhoven RF, et al. Lancet 2009;374(9688):459-66

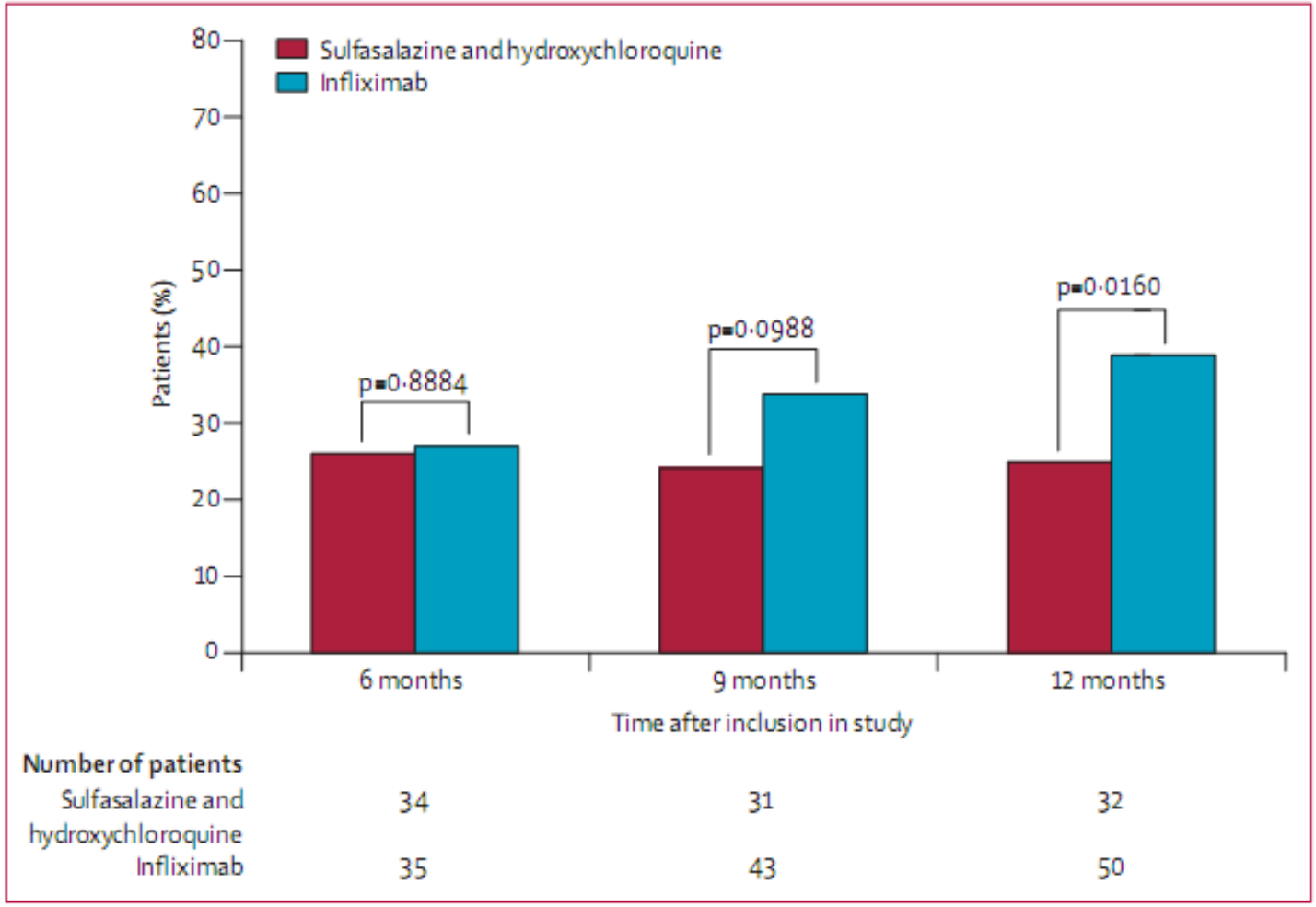


Figure 3: Proportion of patients achieving a good response according to EULAR criteria at 6, 9, and 12 months

van Vollenhoven RF, et al. Lancet 2009;374(9688):459-66

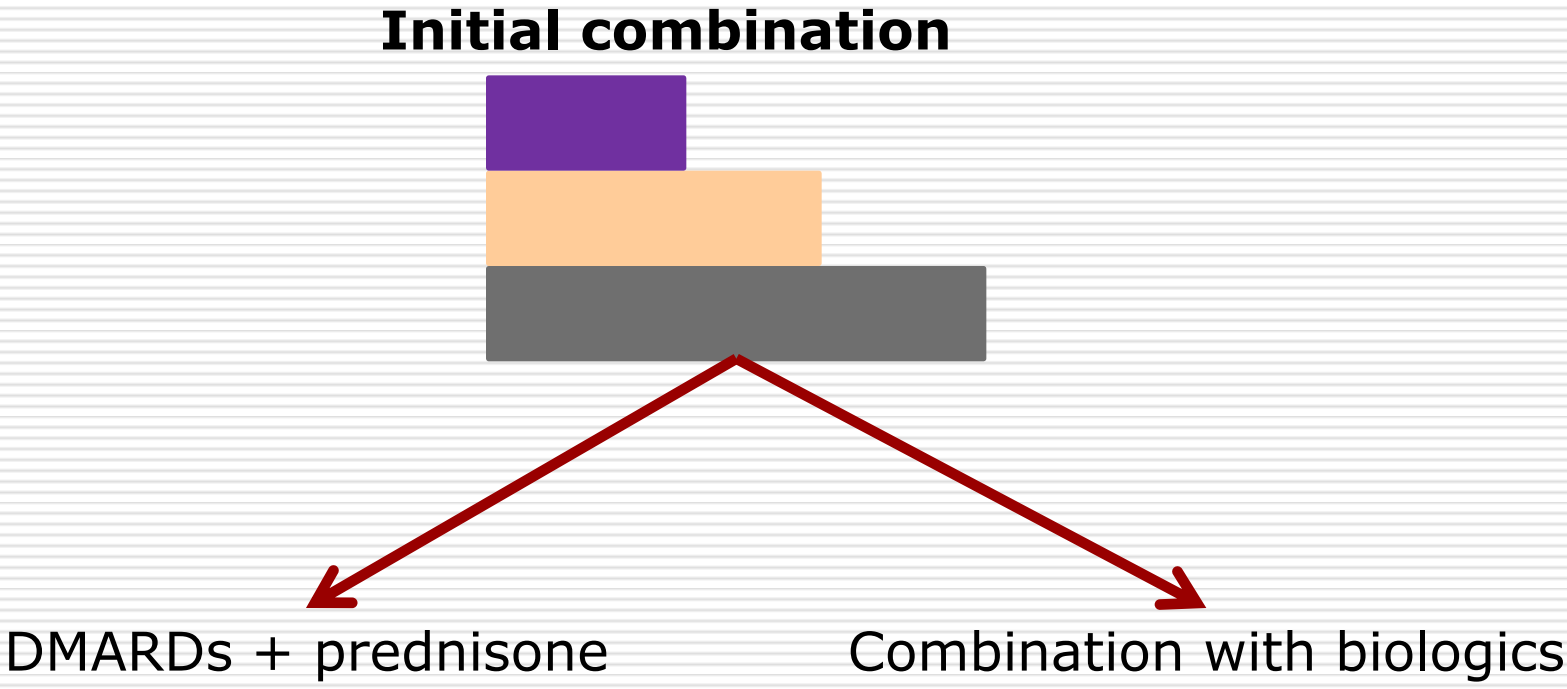
	Sulfasalazine and hydroxychloroquine (n=130)	Infliximab (n=128)
Total adverse events	48	32
Number of patients with at least one adverse event	33 (25%)	26 (21%)
Blood and lymphatic system	5	1
Liver	1	5
Infectious	0	5
Skin and allergic reactions	3	11
Gastrointestinal	15	1
Respiratory system	2	2
Hypertension	2	0
Eyes	2	0
Ears	1	0
Central and peripheral nervous system	6	1
Musculoskeletal	0	1
Psychiatric	4	0
General	2	3
Neoplasms	0	0
Abnormal blood test	1	1
Unspecified	4	1
Serious adverse events	1 (generalised symptoms*)	1(persistentfever)

*Lassitude, fatigue, general aches, and low-grade fever.

Table 3: **Adverse events reported from randomisation to 12 months**

van Vollenhoven RF, et al. Lancet 2009;374(9688):459-66

Strategies of RA treatment



DMARDs combination

- Prednisone
  +
- Methotrexate
  +
- SSZ +/- HCQ

- Prednisone
  +
- Methotrexate
  +
- Cyclosporine-A

- Prednisone
  +
- Methotrexate
  +
- Leflunomide

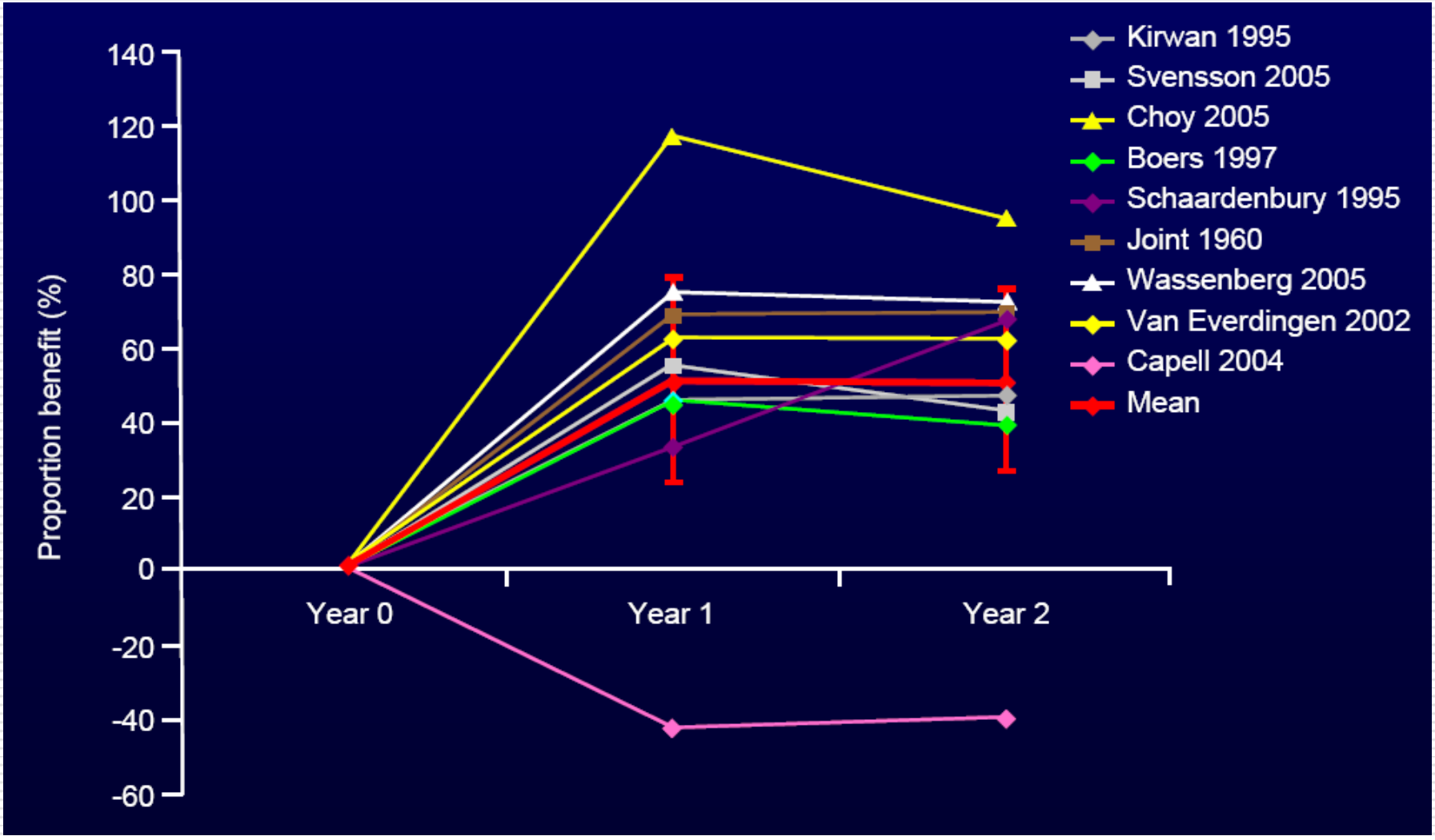
- Prednisone
  +
- Methotrexate
  +
- Biologic agents

Tugwell P et al. N Engl J Med. 1995, Kremer JM et al. Ann Intern Med. 2002,
O'Dell JR et al. Arthritis Rheum 2002 HCQ = hydroxychloroquine

Effects of glucocorticoids on radiological progression in RA (Review)

Kirwan, et al.Cochrane Database of Systematic Reviews 2007 (24 January); Issue 1. No: CD006356.DOI

One- and two-year proportion (%) benefit (two-year studies)



Benefits and risks of steroids

Benefits

- Effective
- Cheap
- Symptomatic relief
- Radiographic slowing
- Recommended in guidelines

Risks

- Bone loss
  - "Non issue" but care gap
- Accelerated atherosclerosis
- Can't always taper
- Not patients' preference
- Prevents access to "appropriate" Tx
- Challenges in diabetic patient
- Other toxicity

Gorter SL, Bijlsma JW, Cutolo M, Gomez-Reino J, Kouloumas M, Smolen JS, Landewé R, et al

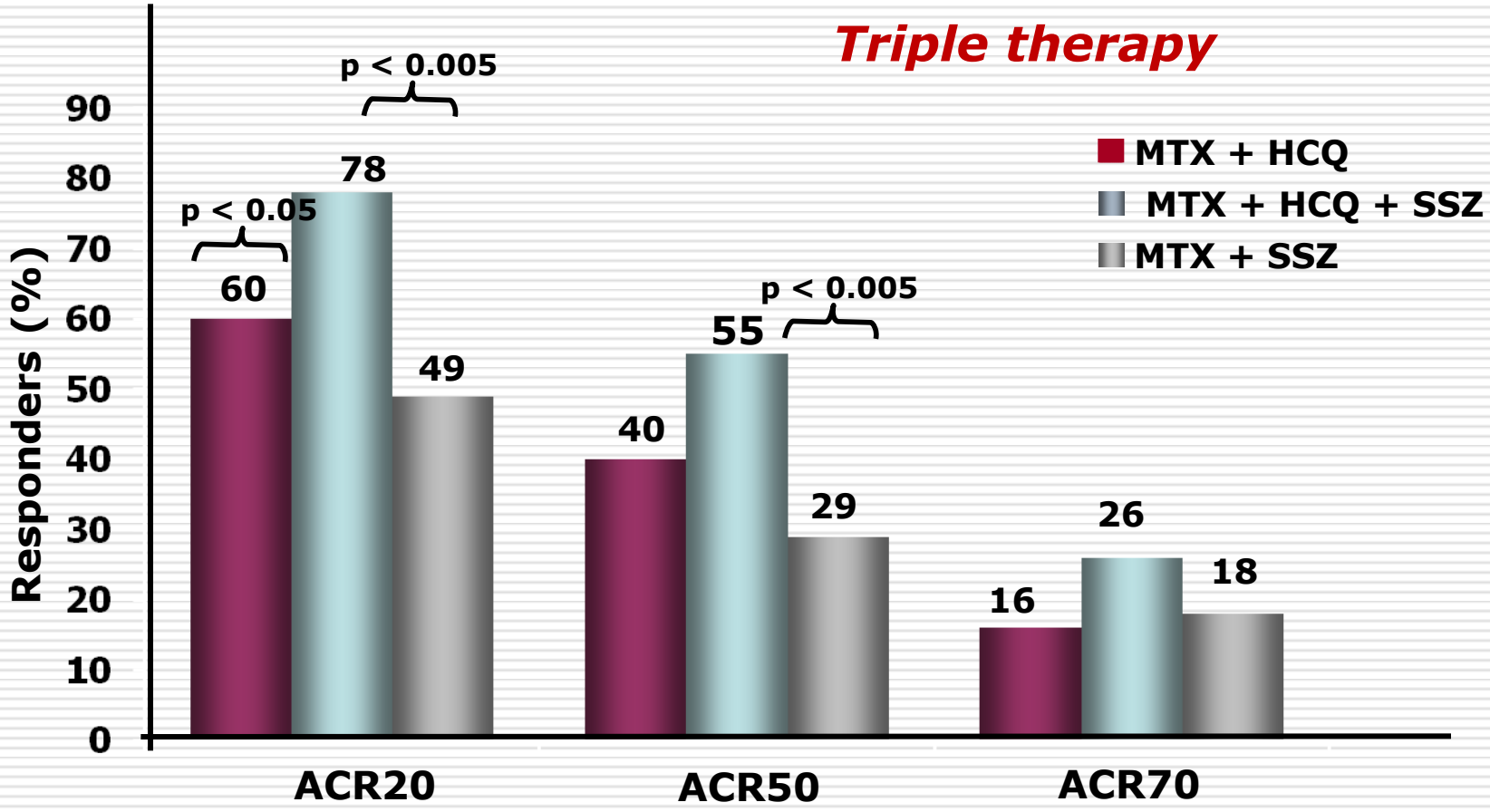
Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis

Ann Rheum Dis 2010;69:1010-4

Conclusion

GCs are effective in relieving signs and symptoms and inhibiting radiographic progression, either as monotherapy or in combination with synthetic DMARD monotherapy or combination therapy

DMARDs combination



HCQ = hydroxychloroquine; SSZ = sulfasalazine.

O'Dell JR, et al. Arthritis Rheum 2002;46:1164-1170.

Smolen JS, Landewé R, Breedveld FC, et al

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs

Ann Rheum Dis 2010;69:964–75

Conclusion

These recommendations are intended to inform rheumatologists, patients and other stakeholders about a European consensus on the management of RA with **DMARDs and GCs** as well as strategies to reach optimal outcomes of RA, based on evidence and expert opinion

Bakker MF, Jacobs JW, Verstappen SM, Bijlsma JW

Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility

Ann Rheum Dis 2007;66(Suppl III):iii56–iii60

Conclusion

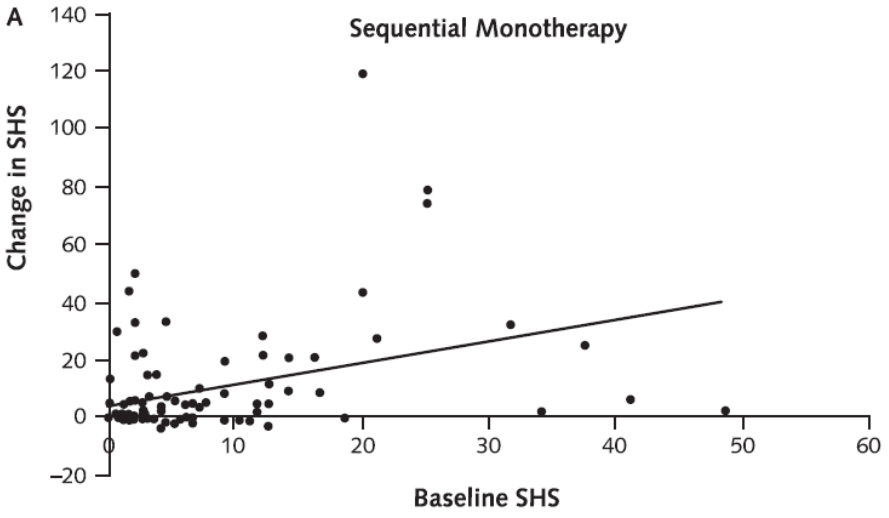
Tight control aiming for low disease activity or even better still, remission, seems a promising option in treating patients with RA in clinical trials and probably also in daily practice

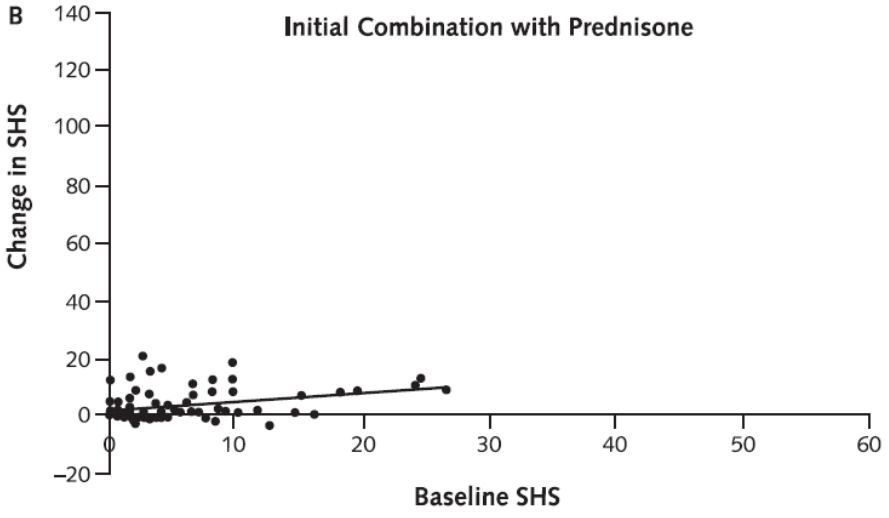
Table 1 Characteristics of the tight control studies

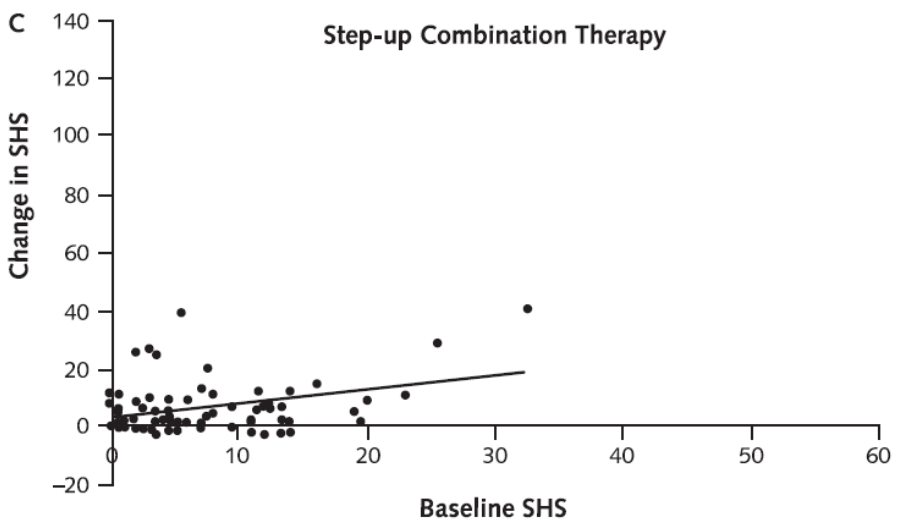
Study	Interventions/groups	n	Medication at the start	Frequency of assessment	Inclusion criteria	Disease duration
FIN-RACo	Combination therapy*	97	SSZ, MTX, HCQ, predn	3 months (variable)	ARA criteria RA, 18–65 yr, symptoms <2 yr, active disease ⩾3 SJ and 3 of: ⩾28 mm/h ESR or ⩾19 mg/l CRP, ⩾29 min/ms, >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)		

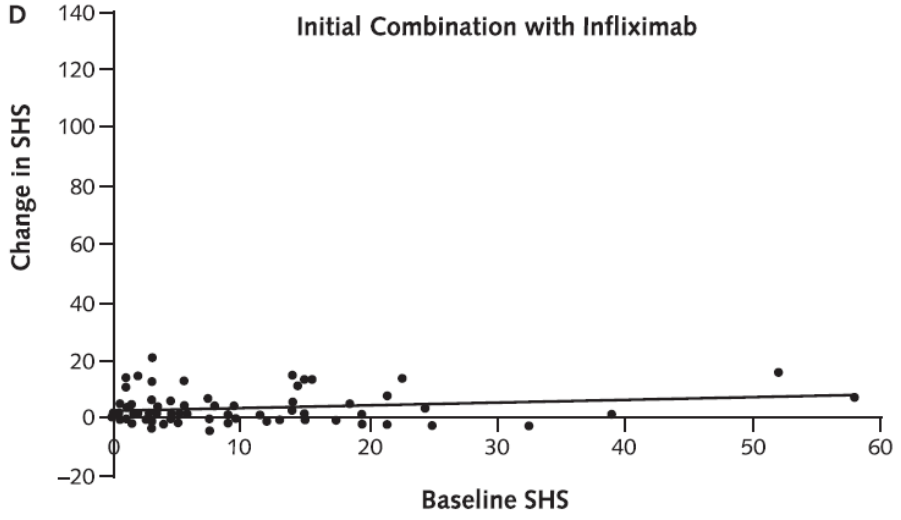
Bakker MF, et al. Ann Rheum Dis 2007;66(Suppl III):iii56–iii60

Figure 4. Median change by baseline total Sharp–van der Heijde score (*SHS*) for the 4 treatment groups.









The solid lines are regression lines.

Goekoop-Ruiterman YPM, et al. Ann Intern Med 2007;146:406-15

Knevel R, Schoels M, Huizinga TW, Aletaha D, et al

Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis

Ann Rheum Dis 2010;69:987-94

Conclusion

Intensive steering strategies and intensive medication strategies produce a better clinical outcome, improved physical function and less structural damage than conventional steering or treatment. Proof in favour of any steering method is lacking and the best medication sequence is still not known

Verstappen SM, Bakker MF, Heurkens AH, et al

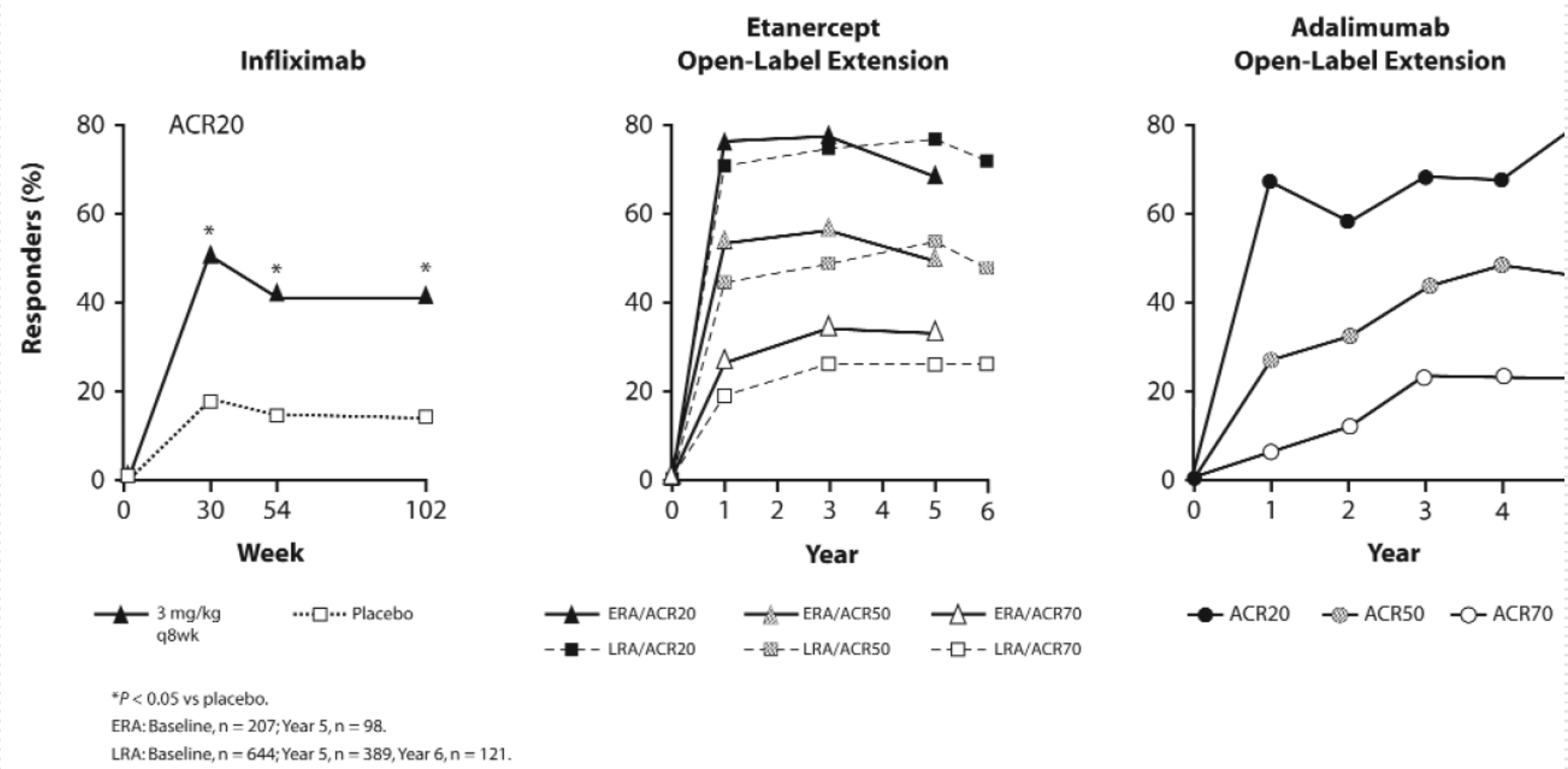
Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with methotrexate tight control therapy: the CAMERA study

Ann Rheum Dis 2010;69:1044-8

Conclusion

Although the occurrence of AEs in the intensive strategy group was higher than in the conventional strategy group, the previously observed clinical efficacy of an intensive treatment strategy seems to outweigh the observed toxicity profiles. **When starting MTX, attention should be given to patients with a high BMI and those with increased levels of liver enzymes and decreased renal function**

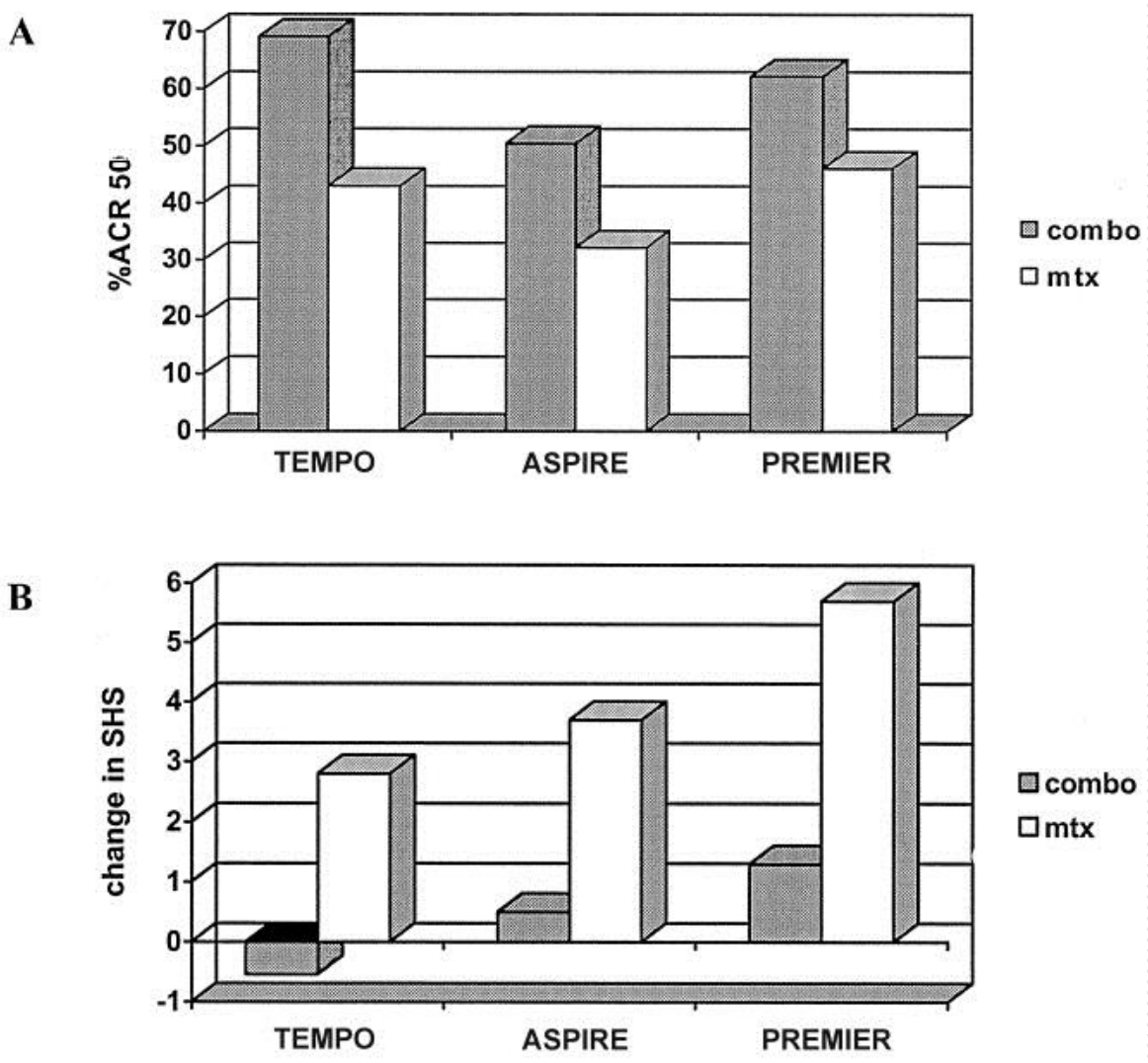
Does the use of anti-TNFα make any difference?



*P < 0.05 vs placebo.
ERA: Baseline, n = 207; Year 5, n = 98.
LRA: Baseline, n = 644; Year 5, n = 389, Year 6, n = 121.

Figure 7. ACR responses in randomized controlled trials[21, 69-72]. ERA: early RA; LRA: late-stage RA.

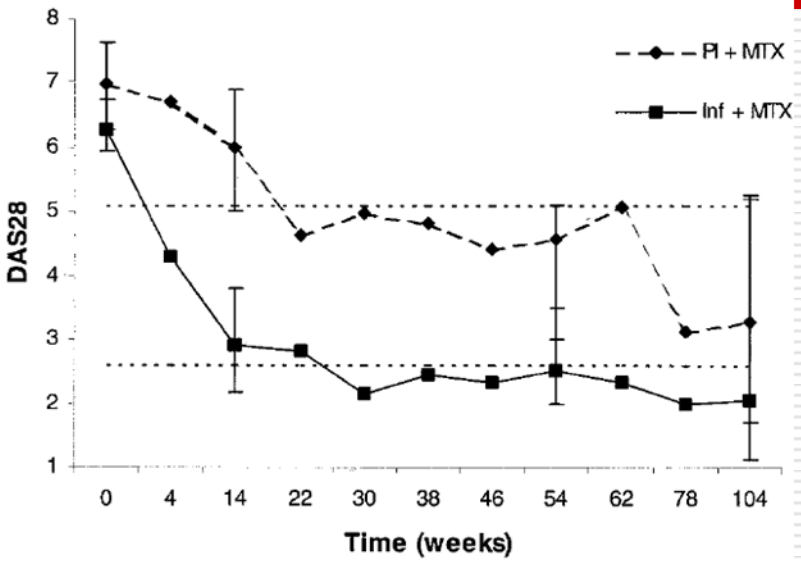
Cohen SB, et al. J Rheumatol 2008;35 (suppl 81):4-30

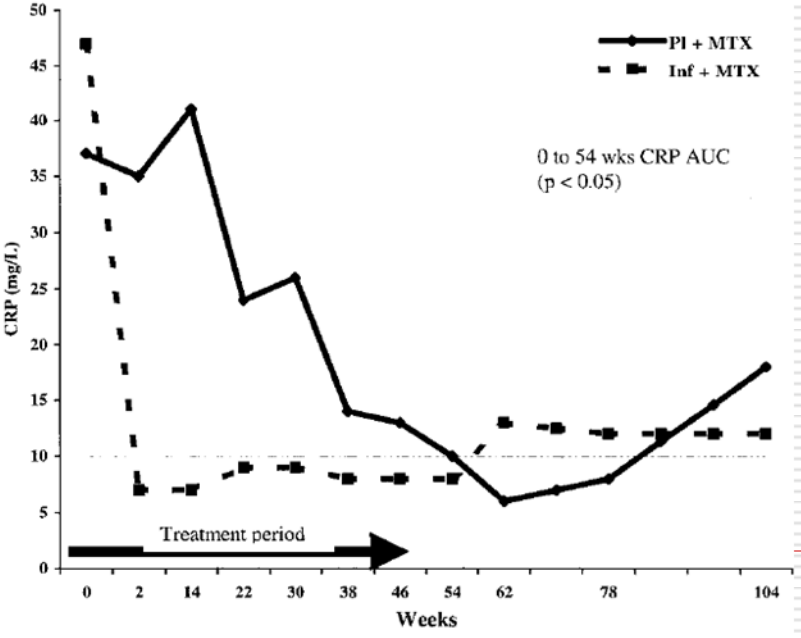


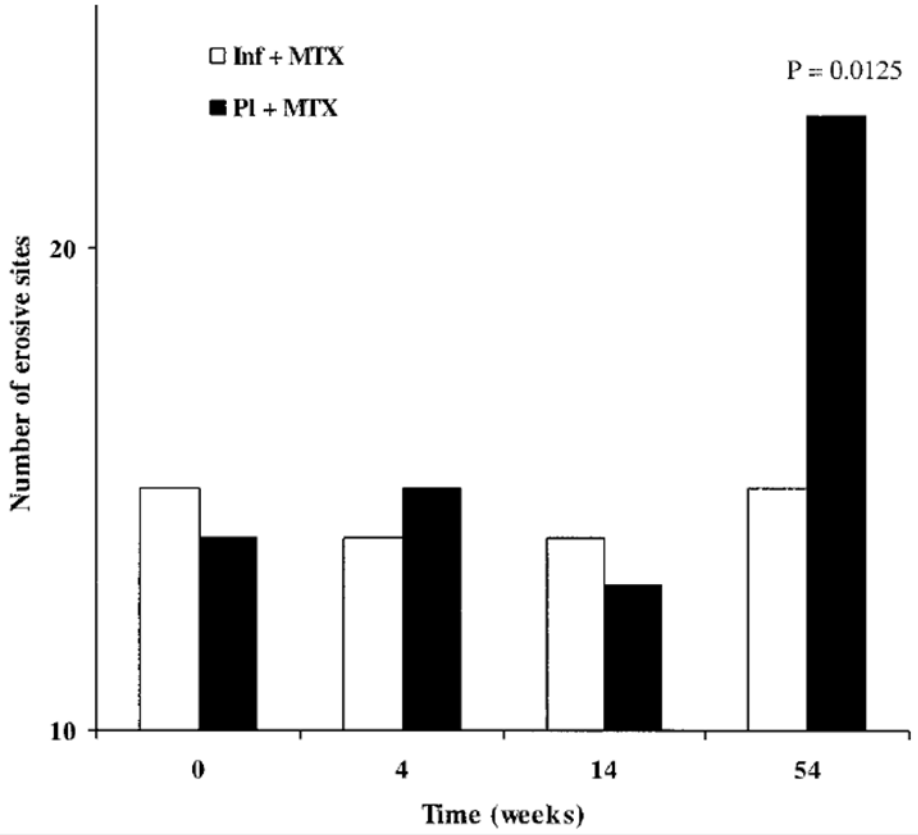
Weisman MH. Arthritis Rheum 2005;52:3326-32

Can we use anti-TNFα agents as first choice?

Infliximab in early RA

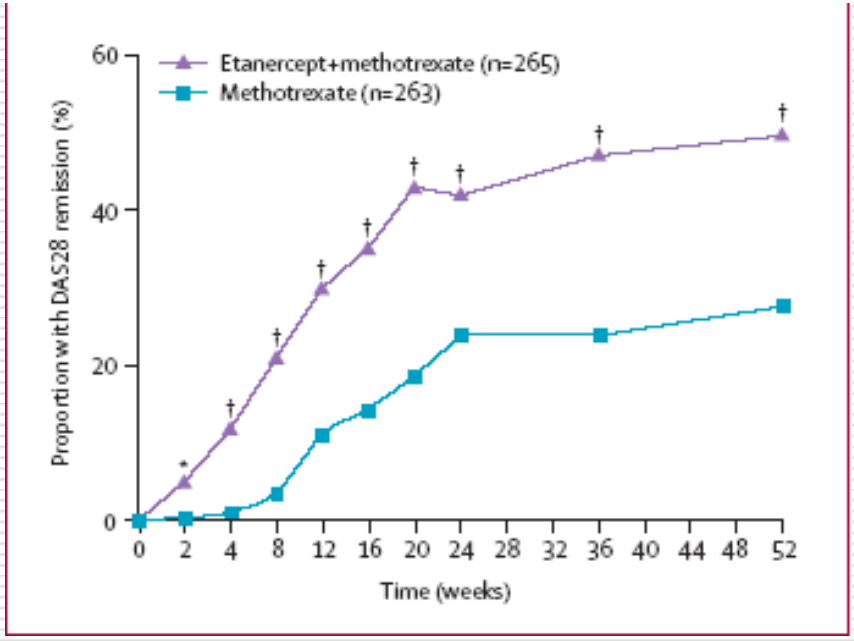




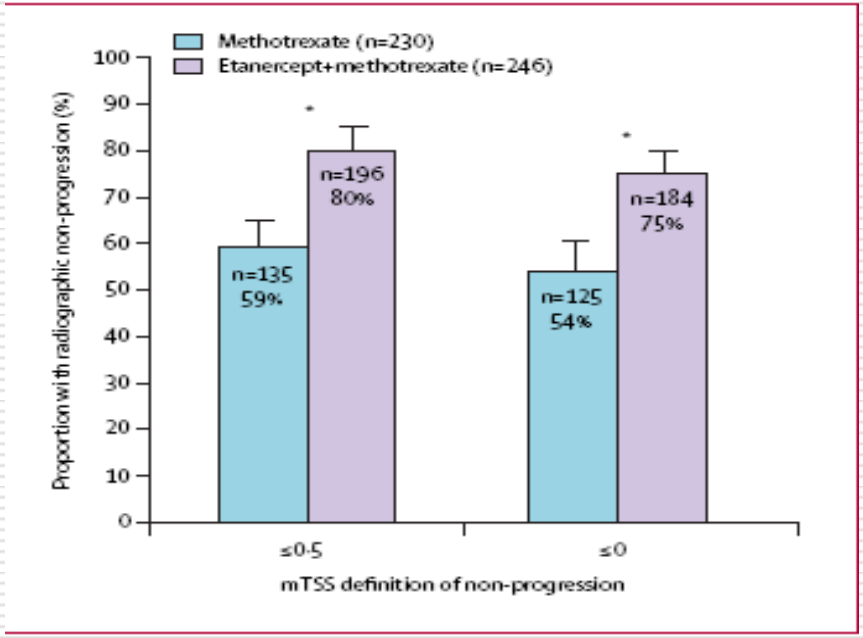


Quinn et al. Arthritis Rheum 2005;52:27-35

Etanercept in early RA (COMET trial)



DAS28 remission over 52 weeks of treatment



Proportions of patients achieving radiographic non-progression at week 52

Emery P et al. Lancet 2008; 372: 375–82.

TNF Antagonists "Window of Opportunity?" in early disease

- Anti-TNF better as first line, but sufficient to justify cost?

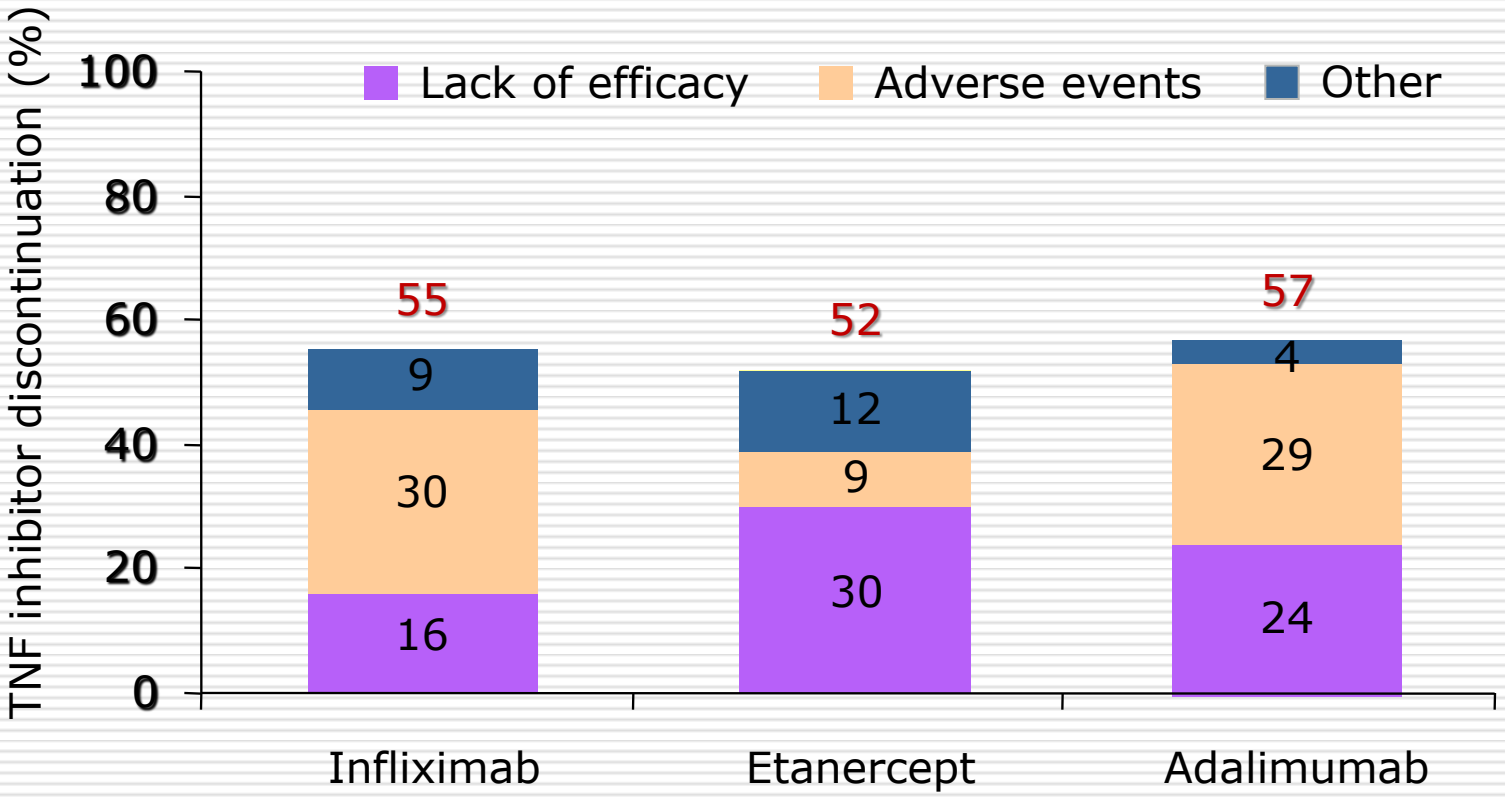
Need to show

1. Unique benefit
2. Unique damage prevention
3. Able to withdraw therapy and maintain benefit
4. Prevent job loss

Fail a TNF antagonist?

- Switch TNF agent?
- New biologic?

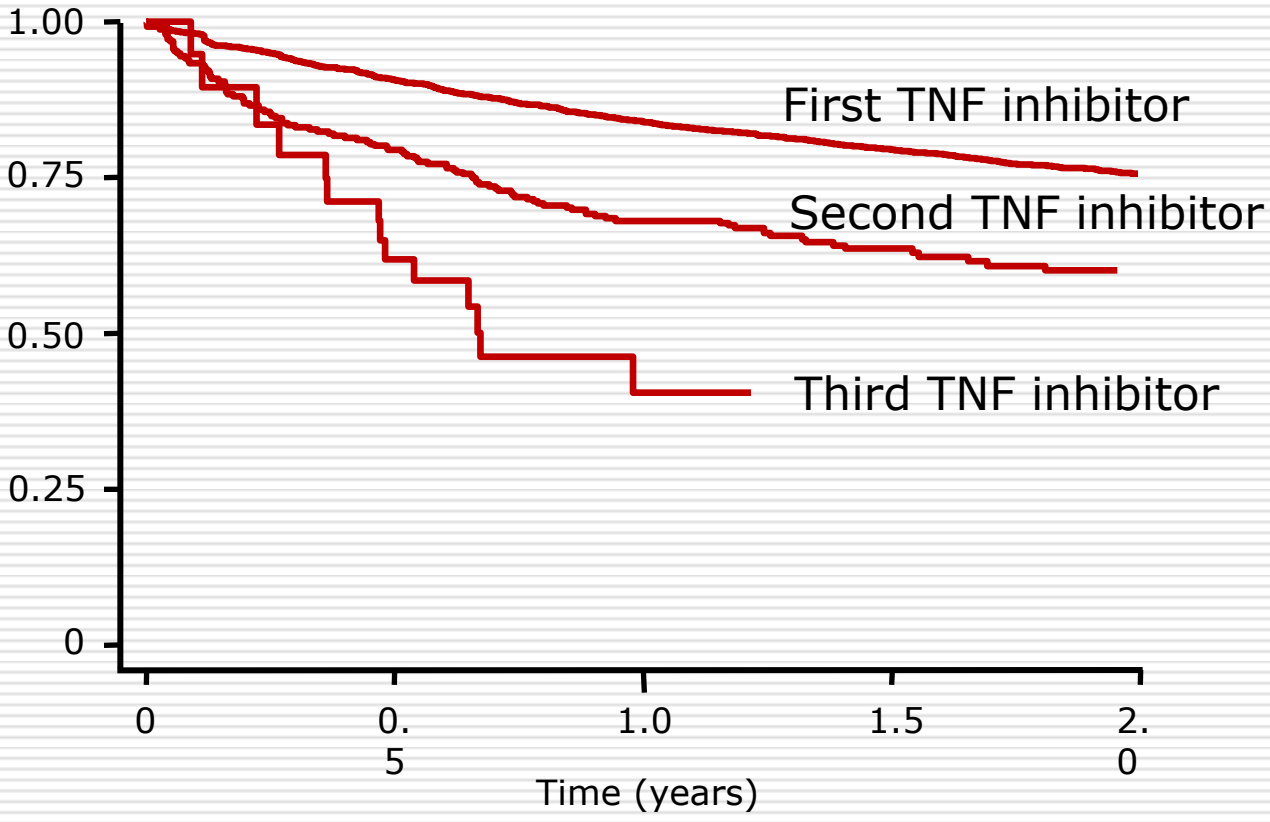
Discontinuation of TNF inhibitors: Dutch registry



Maximum follow-up duration for infliximab, adalimumab and etanercept was 45, 79 and 42 months

Flendrie, et al. Ann Rheum Dis 2006;65(Suppl. II):191

Survival of TNF Inhibitors After Switching



Gomez-Reino, et al. Arthritis Res Ther 2006;8:R29

Papagoras C, Voulgari PV, Drosos AA

Strategies after the failure of the first anti-tumor necrosis factor alpha agent in rheumatoid arthritis

Autoimmun Rev 2010;9:574-82

Does the use of other biologics make any difference?

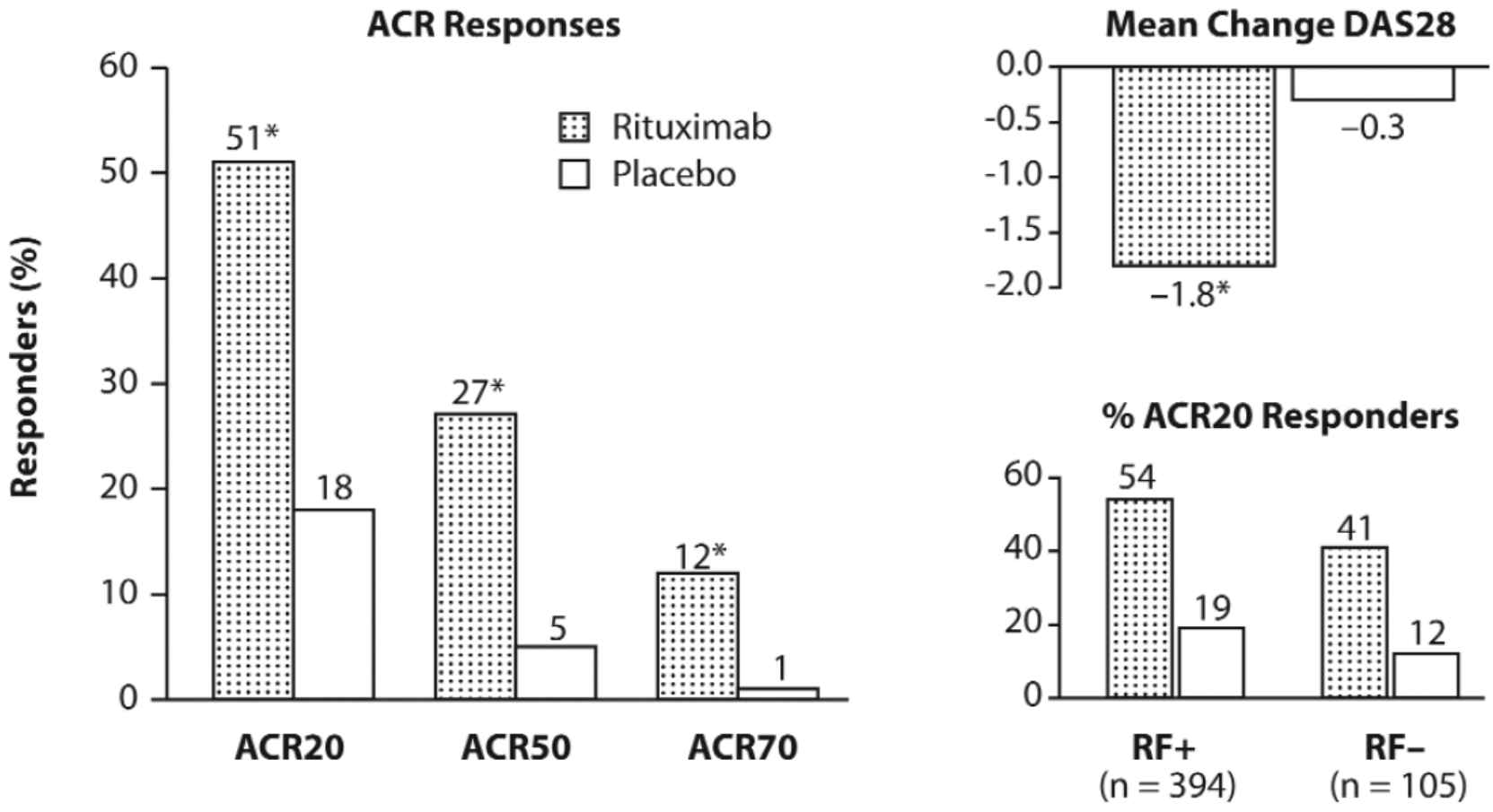
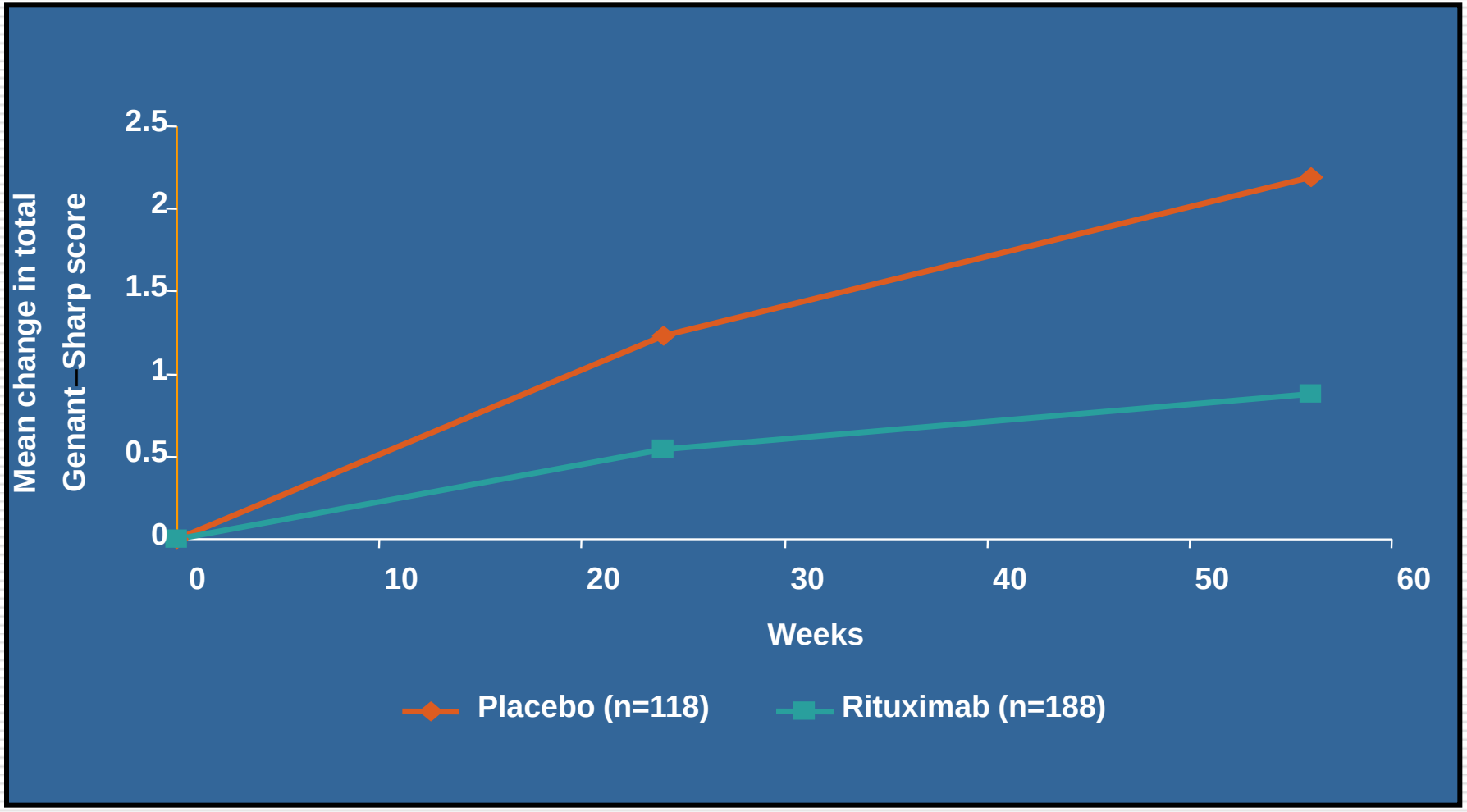


Figure 9. Clinical response at 24 weeks[8,105]. *P<0.0001.

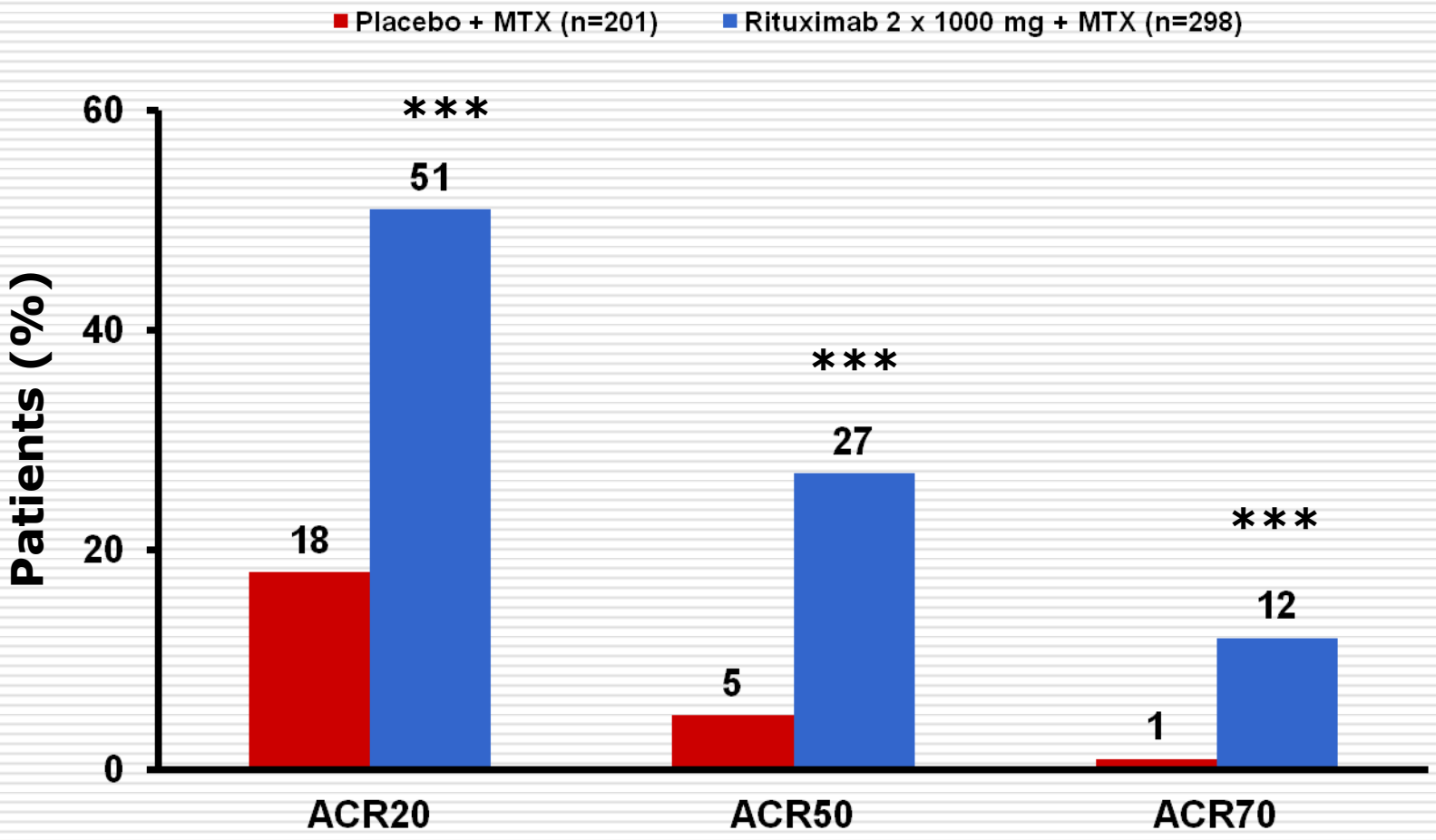
Mean change in total Genant–Sharp score over time



Observed analysis including patients with radiographs at baseline, Week 24 and Week 56

Keystone et al. Ann Rheum Dis 2006;65(S2):58

Rituximab (REFLEX): ACR responses at Week 24 in patients who previously failed TNF inhibitors



***p<0.0001 vs placebo

Cohen et al. Arthritis Rheum 2006;54:2793–806

Annals of Internal Medicine | ARTICLE

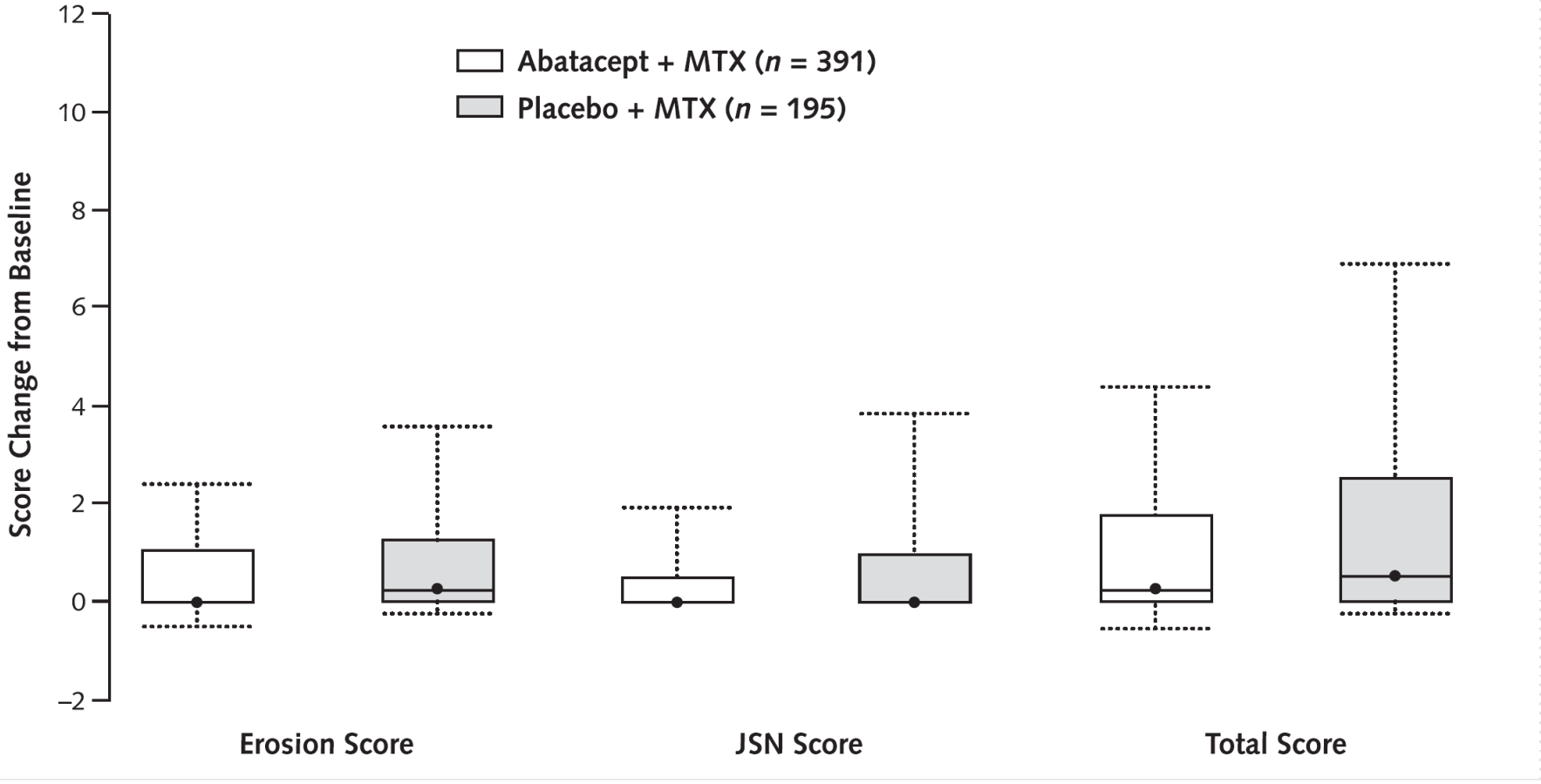
Effects of Abatacept in Patients with Methotrexate-Resistant Active Rheumatoid Arthritis

A Randomized Trial

Joel M. Kremer, MD; Harry K. Genant, MD; Larry W. Moreland, MD; Anthony S. Russell, MD; Paul Emery, MD; Carlos Abud-Mendoza, MD; Jacek Szechinski, MD; Tracy Li, PhD; Zhiyu Ge, PhD; Jean-Claude Becker, MD; and Rene Westhovens, MD

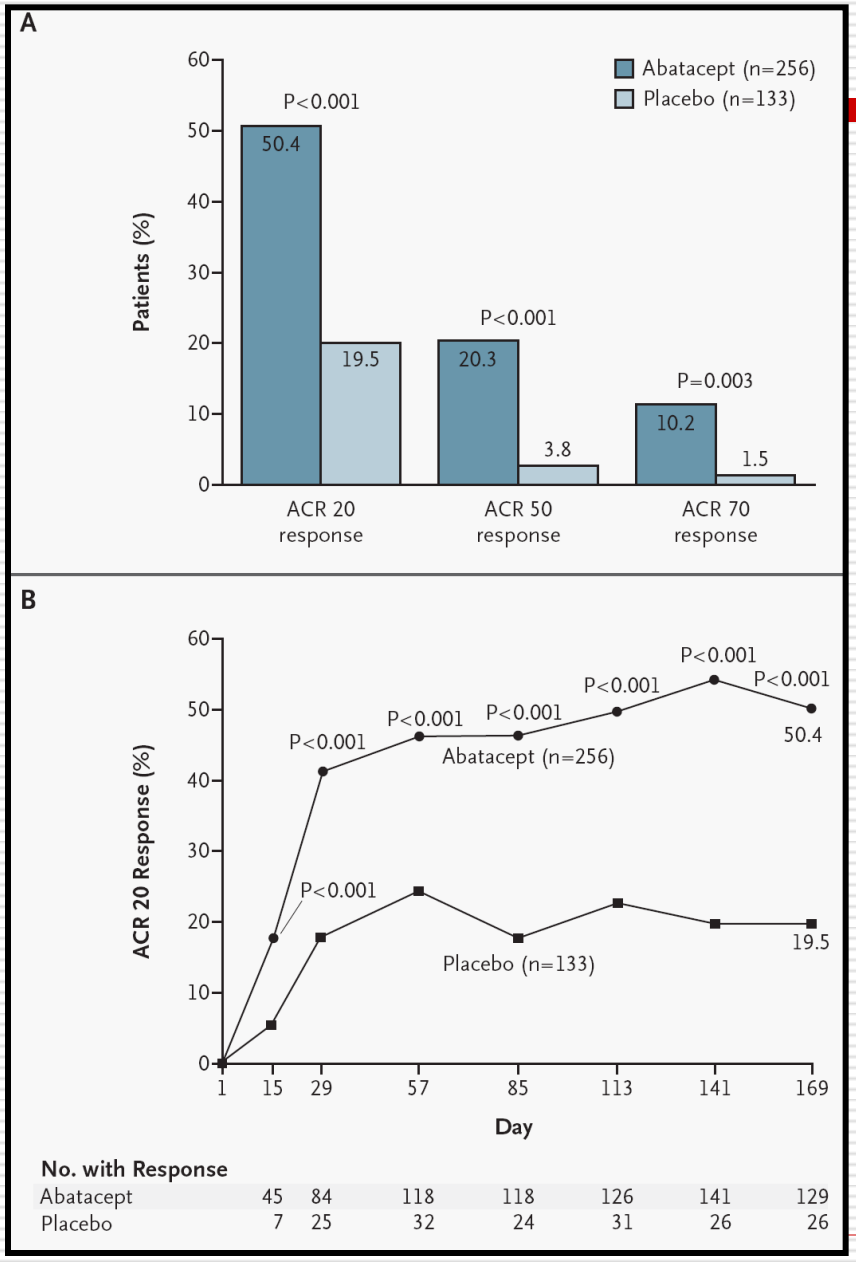
- Study design:
  - Abatacept (10mg/Kg) + MTX, n=385
  - Placebo + MTX, n=162
- End points:
  - ACR20, ACR50, ACR70
  - DAS28
  - HAQ, SF36
  - Genant modified Sharp Score

Abatacept in RA patients resistant to MTX



Kremer et al, Ann Intern Med 2006

Abatacept in refractory anti-TNF therapy in RA



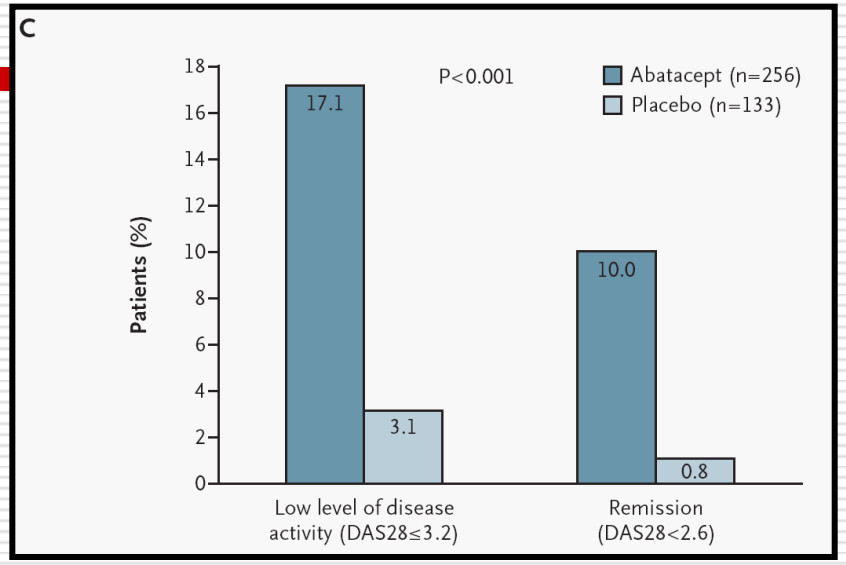
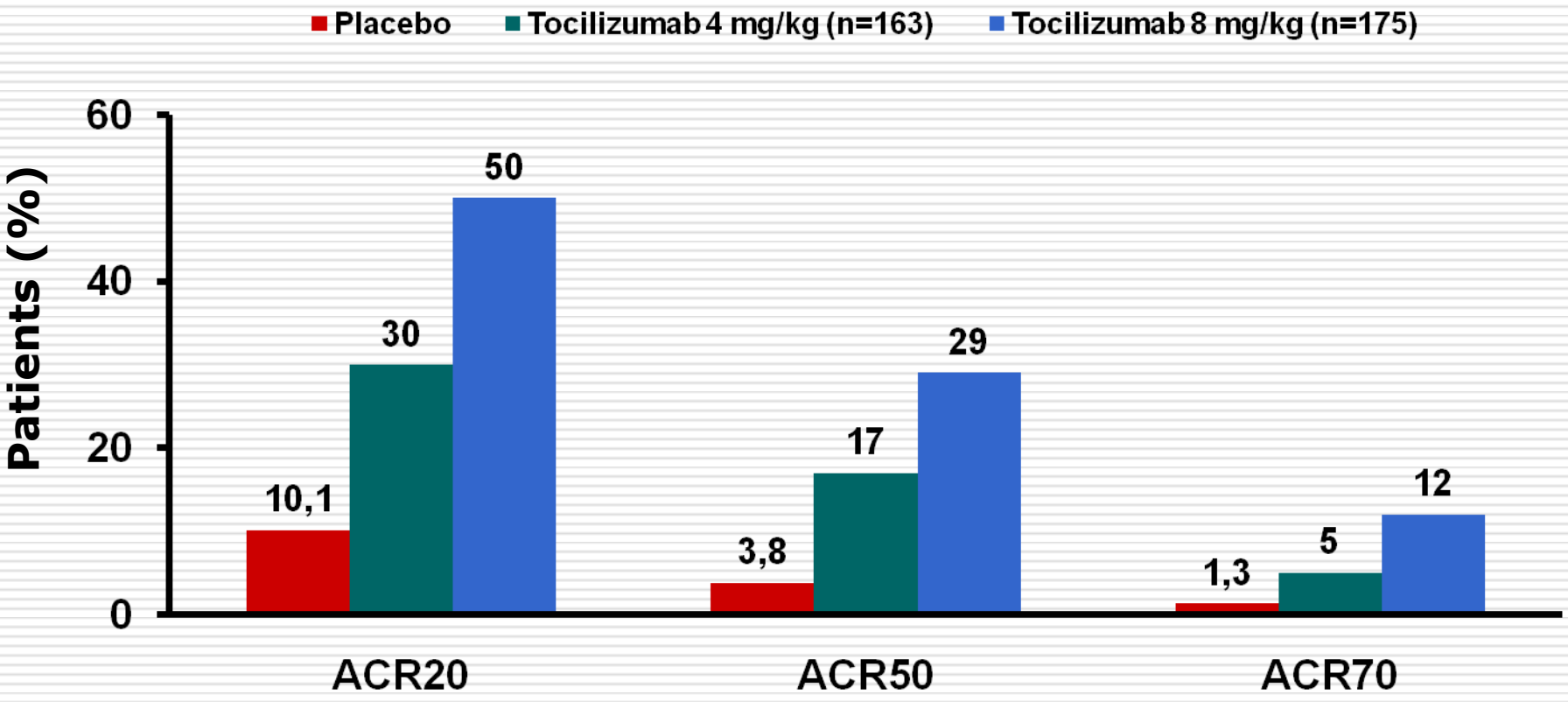


Figure 2. Signs and Symptoms of Disease.

Panel A shows the rates of ACR 20, ACR 50, and ACR 70 responses at six months. Panel B shows the rates of ACR 20 responses at each post-baseline visit during the six-month study. The numbers below the panel are the numbers of patients with a response who were assessed. Panel C shows the rates of low levels of disease activity and remission at six months as defined with the use of the DAS28. Two patients in the abatacept group were excluded from the efficacy analysis because of a protocol violation.

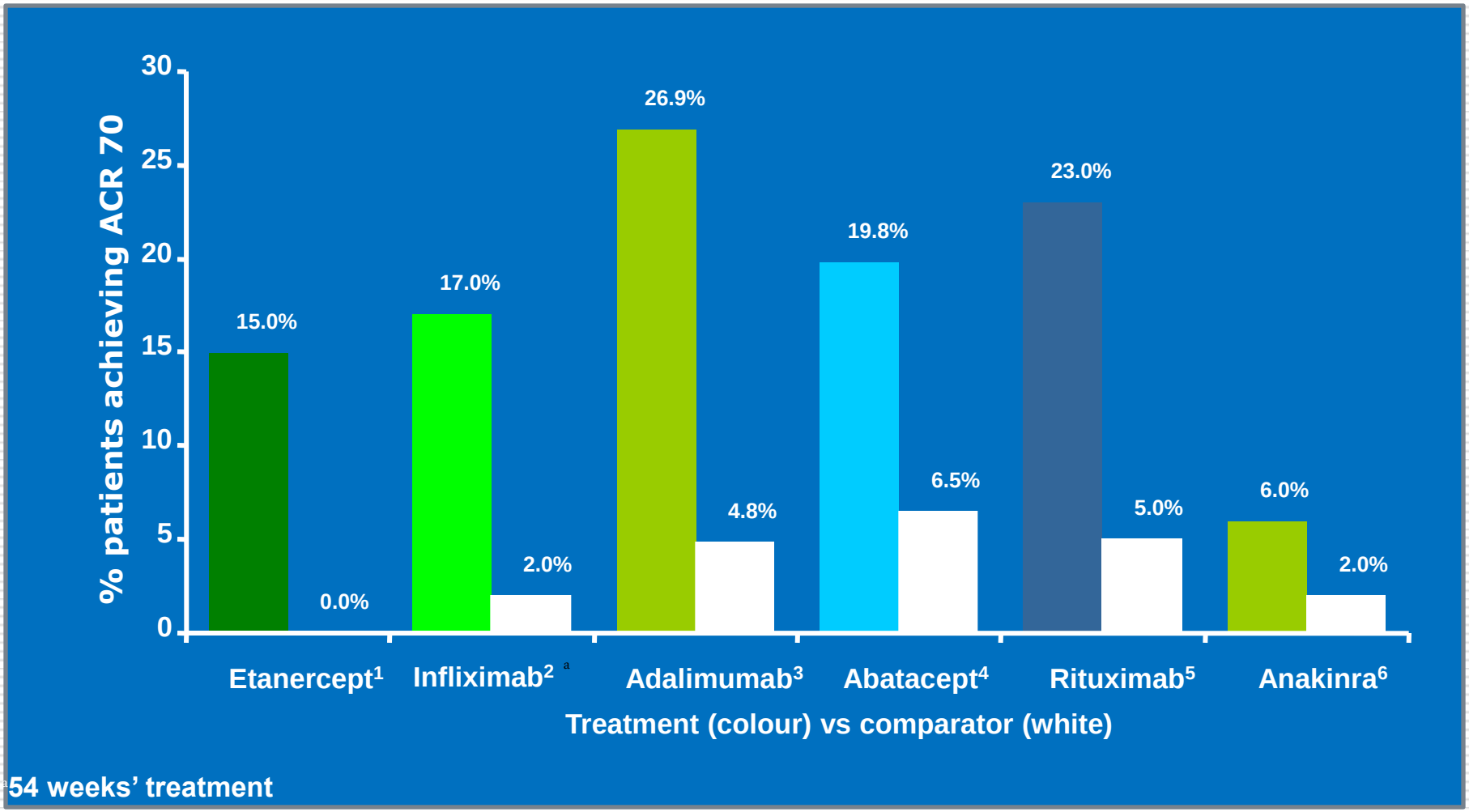
Genovese MC, et al. N Engl J Med 2005;353:1114-23

Tocilizumab (RADIATE): ACR responses at Week 24 in patients who had received ≥1 TNF inhibitor



Emery et al. Ann Rheum Dis 2008;67:1516–1523

Biological + MTX versus MTX monotherapy ACR70 at 6 months



[1]Weinblatt, et al. N Engl J Med 1999;340:253–259; [2]Lipsky, et al. N Eng J Med 2000;343:1594–1602; [3]Weinblatt, et al. Arthritis Rheum 2003;48:35–45; [4]Kremer, et al. Ann Int Med 2006;144:865–876; [5]Edwards, et al. N Engl J Med 2004;350:2572–2581.; [6]Cohen, et al. Ann Rheum Dis 2004;63:1062–1068

Nam JL, Winthrop KL, van Vollenhoven RF, et al

Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA

Ann Rheum Dis 2010;69:976-86

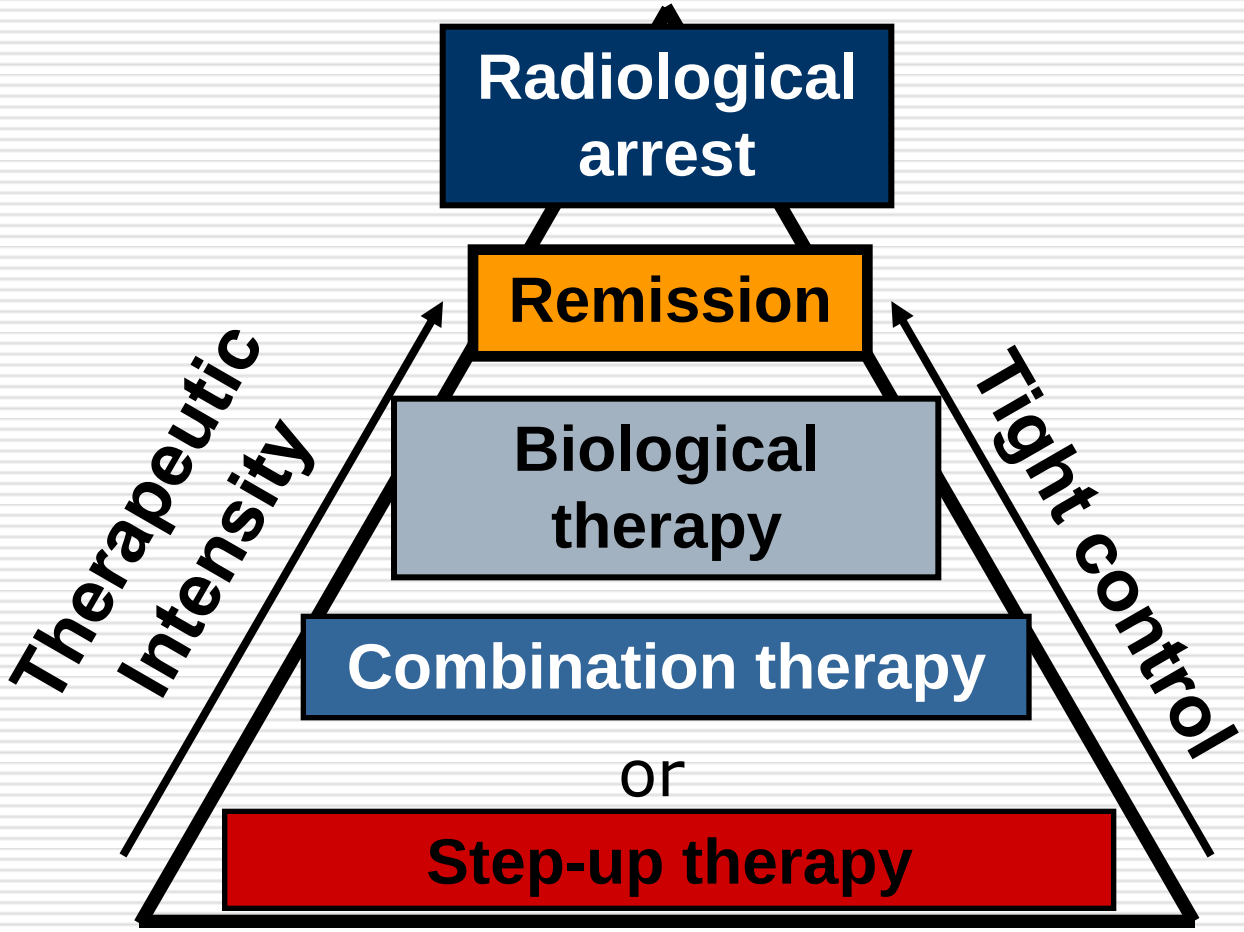
Conclusion

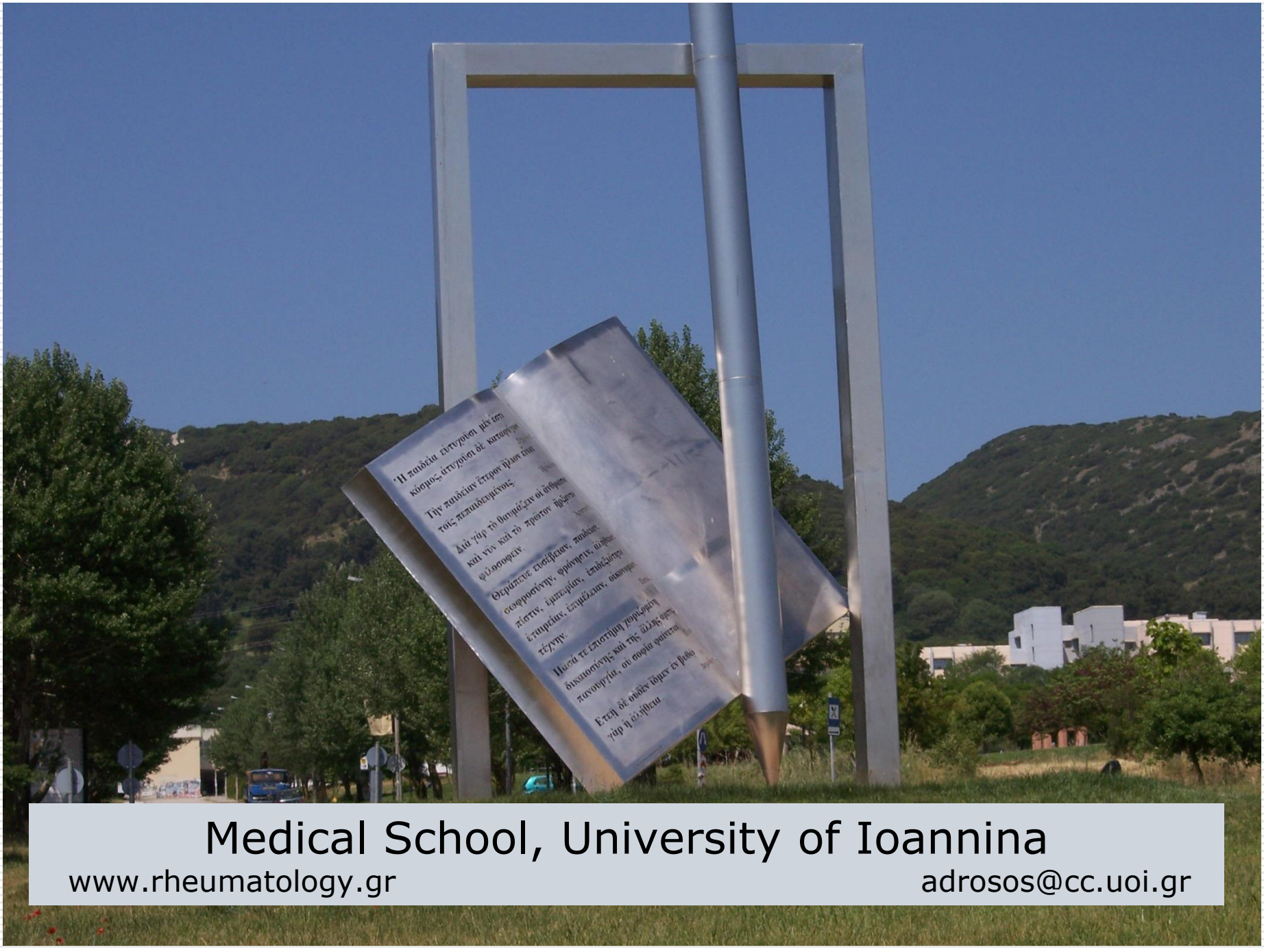
There is good evidence for the efficacy of biological agents in patients with RA. Safety data confirm an increased risk of bacterial infection and TB with TNFi compared with conventional DMARDs

Conclusions

- Treatment practices are those that help patients achieve objective treatment goals
  - Remission of disease activity
  - Arrest of radiographic progression
  - Normal QoL
- Tight disease control
- Individualized treatment strategies
- Now there are more tools to reach these goals
- New targeted therapies can help more patients

Increased therapeutic intensity and tight control lead to remission in RA





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