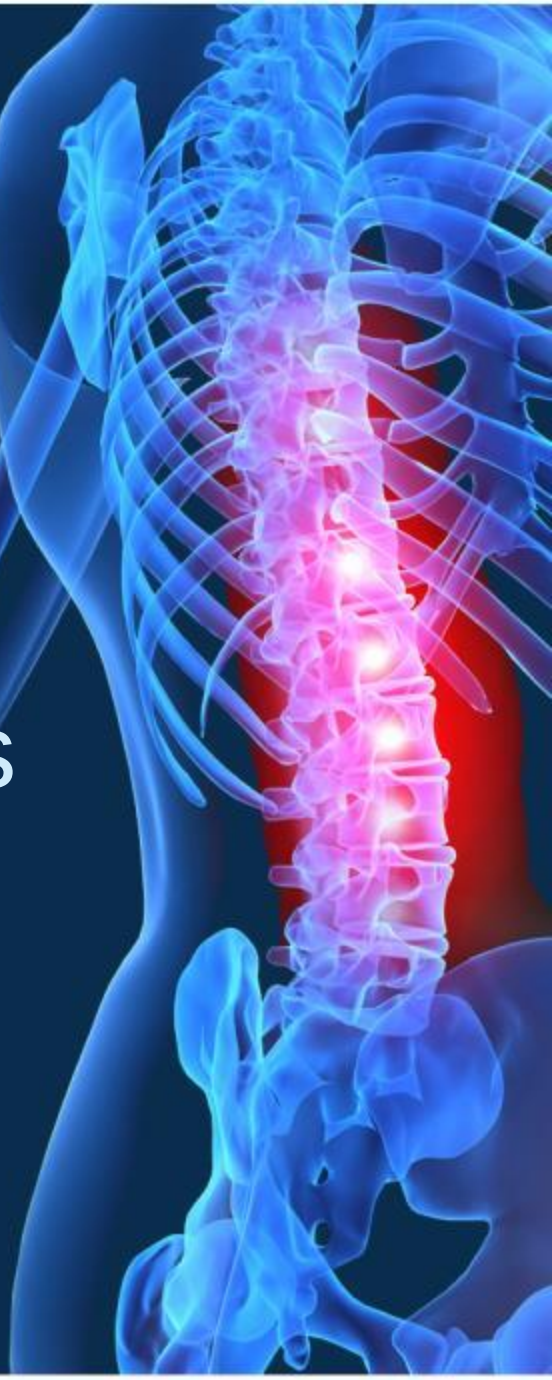
Annual Rheumatology & Therapeutics Review for Organizations & Societies



RA: Update on Biologic Therapy and Step-Up or Step-Down Therapeutic Options

Learning Objectives

- Describe the importance of remission in clinical trials and practice
- Discuss the importance of step-up (combination) therapy in RA

Step Up or Step Down - Outline

- Arguments for Step-up & Step-down
  - Why go up/down
  - Physician changes w/ active & inactive disease
- Combination is king
- Drug withdrawal is achievable
- Likelihood of Remission in RA

Rheumatoid Arthritis and DMARD Rx

Impact of Rheumatologist Care

"…every patient with established, active RA must be treated with a DMARD"

—F Wolfe

- I996-2004 cohort study: 5864 RA Medicare patients[1]
  - 33% saw a rheumatologist in the first 12 months
  - Only 30% received a DMARD in 1st Yr. (53% if seen by a Rheum)
  - DMARD use has grown = **24%** in 1996 → **43%** in 2003
    - if seen by a Rheum = **41%** in 1996 → **70%** in 2003
- 2004-2008 retrospective claims study of 26,911 newly Dx RA pts[2]
  - 63% were given a DMARD within the first 12 months
  - DMARD initiation was higher in those seen by a Rheumatologist
- NEED 3rd Study from 2009-14

1. Schmajuk G, et al. Arthritis Rheum. 2007;57(6):928-934. 2. Bonafede MM, et al. Clin Ther. 2012;34(2):457-467.

Patient Barrier: Unwillingness to Change Therapy

- Survey of 6135 patients with RA enrolled in the National Data Bank for Rheumatic Diseases
- 77.3% were satisfied with their medications, while 9.4% were dissatisfied
- 63.8% would not want to change therapy as long as their condition didn't get worse
  - Despite side effects occurring in 22.4% of the patients during the previous 6 months and in 65.5% at some period during their lifetime
- Predictors of unwillingness to change
  - Satisfaction with RA control (OR 6.8 [95% CI, 5.8-8.0])
  - Risk of side effects (OR 4.4 [95% CI, 3.8-5.2])
  - Physician opinion (OR 1.9 [95% CI, 1.6-2.2])
  - Fear of loss of control (OR 1.8 [95% CI, 1.6-2.1])
  - Costs (OR 1.3 [95% CI, 1.1-1.6])

OR=odds ratio.

1. Wolfe F, Michaud K. Arthritis Rheum. 2007;56(7):2135-2142.

Patient Reluctance to Take Medications

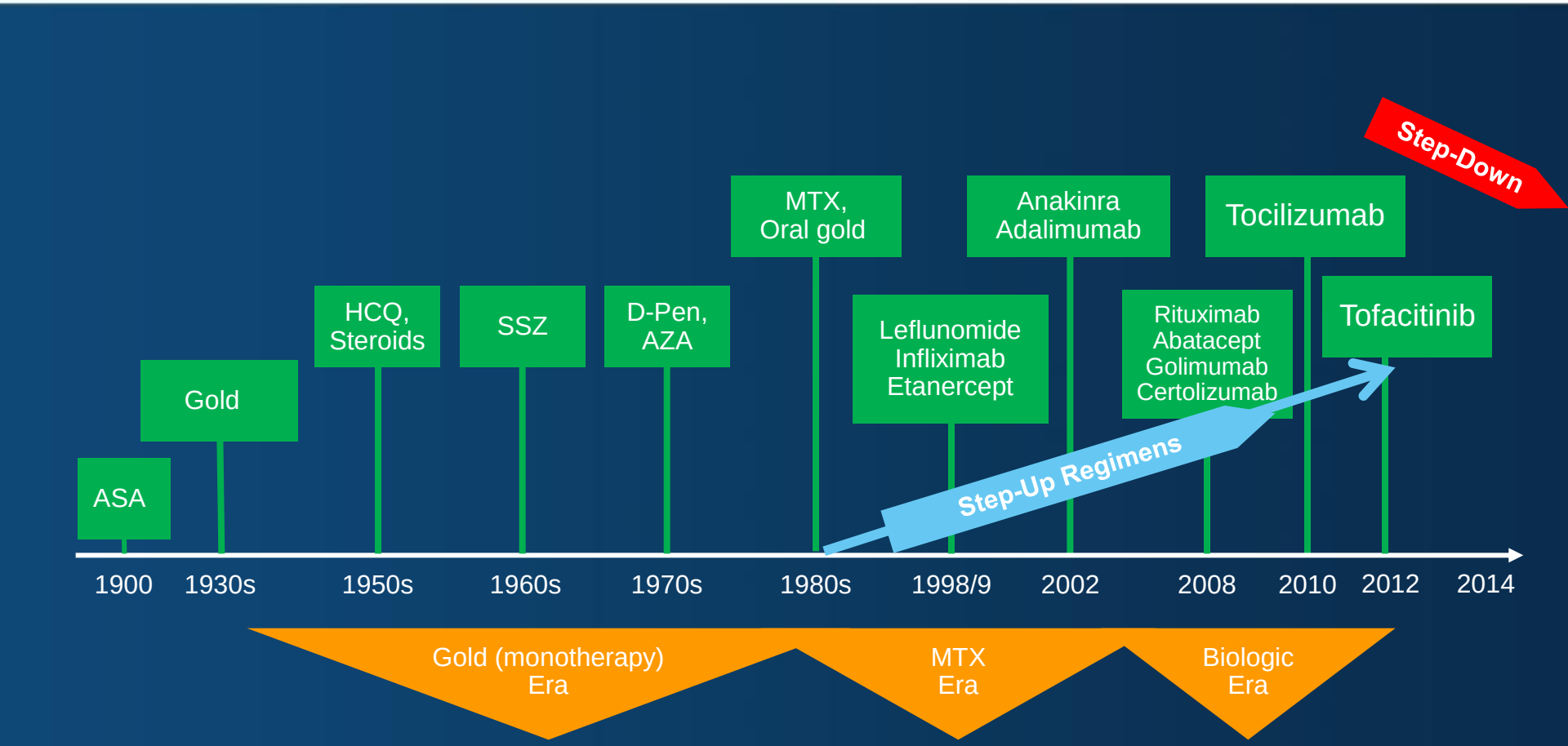
- I’m too old to receive aggressive therapies
- I’m too young to receive aggressive therapies
- MTX/DMARDs/Biologics will affect my fertility
- MTX/DMARDs/Biologics will immunosuppress me
- I don’t like taking (try to avoid) medications
- MTX is a chemotherapy drug
- I’m already taking too many pills
  - #Pills = how unwell (sick) I am (I don’t want to be sick)

Withdrawal Rates on TNF Inhibitor Therapy

Study/Yr	TNF	N	W/D rate	Period	Annual W/D rate
Klareskog 2002	E	1442	29%	3 yrs	10 %
Kristensen 2006	E	309	38%	5 yrs	7.5 %
Kristensen 2006	I	640	58%	5 yrs	10.2 %
Carmona 2006	All	5530	40%	4 yrs	10 %
Flendrie 2003	All	230	50%	5 yrs	10 %
Cruyssen 2006	I	511	37%	4 yrs	9.2 %

E=etanercept; I=infliximab; All=etanercept, infliximab, adalimumab

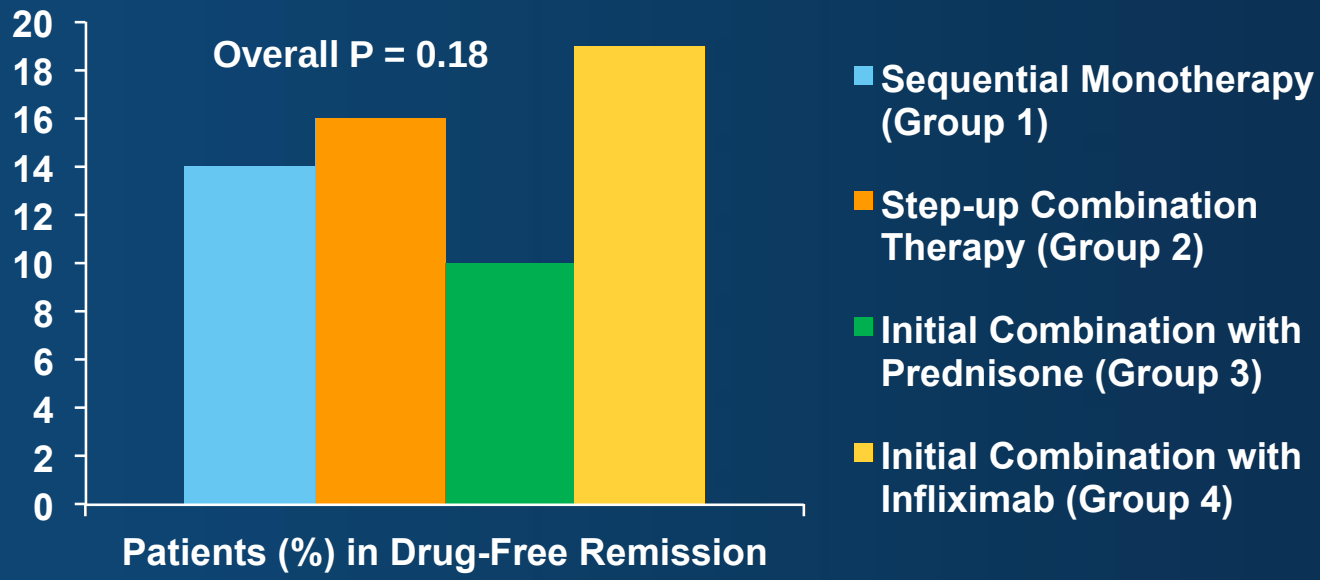
Evolution of RA Treatment



SSZ -

The Promise of Drug-Free Remission in Early RA Results from BeST Study

- BeST study: after 5 yrs – 48% of patients in clinical remission (DAS <1.6)
- 14% in DRUG FREE Remission
- 78% of patients in sustained drug-free remission (≥1 year) demonstrated no radiographic joint damage progression



- With dynamic treatment, up to 19% of patients can achieve drug-free remission, irrespective of the initial approach

Klarenbleek NB et al. Ann Rheum Dis 2011;70:1039–1046.

1981 American College of Rheumatology (ACR) Criteria for Remission

- The ACR criteria for clinical remission in rheumatoid arthritis
- Five or more of the following requirements must be fulfilled for at least 2 consecutive months
  1. Duration of morning stiffness not exceeding 15 minutes
  2. No fatigue
  3. No joint pain (by history)
  4. No joint tenderness or pain in motion
  5. No soft tissue swelling in joints or tendon sheaths
  6. Erythrocyte sedimentation rate (Westergren method) < 30 mm/h for a female or 20 mm/h for a male

Pinals R. Arthritis Rheum 1981; 24:1308-15.

2011 ACR / European League Against Rheumatism (EULAR) Criteria

- ACR/EULAR 2011 Provisional Definitions of Remission for Clinical Trials
- Boolean Based Definition
  - At any time point, a patient must satisfy all of the following:
    - Tender Joint Count ≤1
    - Swollen Joint Count ≤1
    - C-reactive protein (CRP) ≤1 mg/dL
    - Patient Global Assessment ≤1 (on a 0-10 scale)
- Index Based Definition
- At any time point, a patient must have SDAI ≤3.3

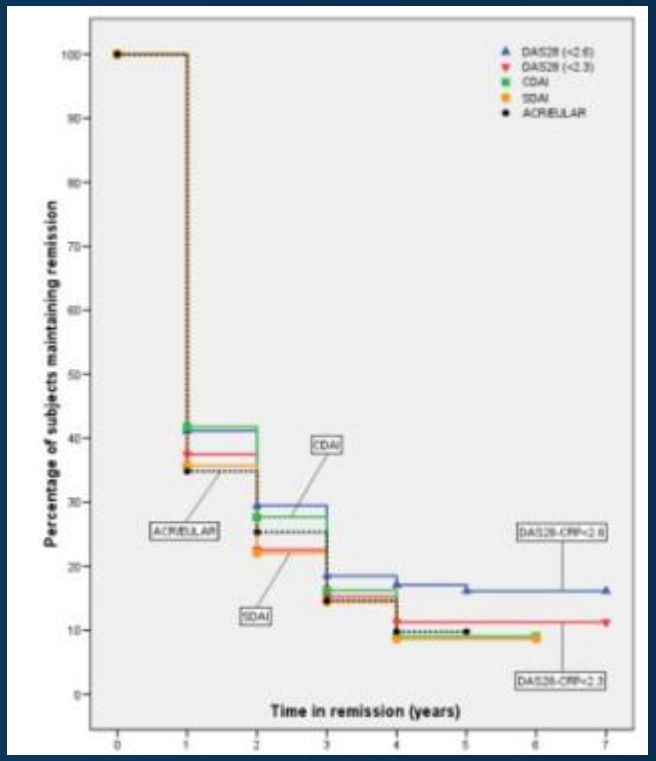
RA Remission in Clinical Practice

Data from BRASS Register

- 394/871 achieved some remission
  - But < 50% stayed in remission 12 mos later
  - Median remission time=1 yr

Number of subjects categorized according to time spent in remission divided by duration, for each of the remission criteria tested

	All subjects in BRASS with ≥2 years of follow-up			
Time in remission (%)	**DAS28-CRP < 2.6** ***N* = 871[a]**	**DAS28-CRP < 2.3** ***N* = 871[a]**	**SDAI** ***N* = 871[a]**	**CDAI** ***N* = 87**
0	326 (37%)	401 (46%)	599 (69%)	610 (70
1-25	130 (15%)	146 (17%)	94 (11%)	30 (3%
26-50	196 (23%)	163 (19%)	108 (12%)	127 (15
51-75	121 (14%)	102 (12%)	52 (6%)	66 (8%
76-99	52 (6%)	30 (3%)	10 (1%)	17 (2%
100	46 (5%)	29 (3%)	8 (1%)	21 (2%
Overall mean time in remission	31%	24%	12%	15%



Prince FHM. Arthritis Res Ther. 2012; 14(2): R68

BARFOT: Long Term Remission in Practice

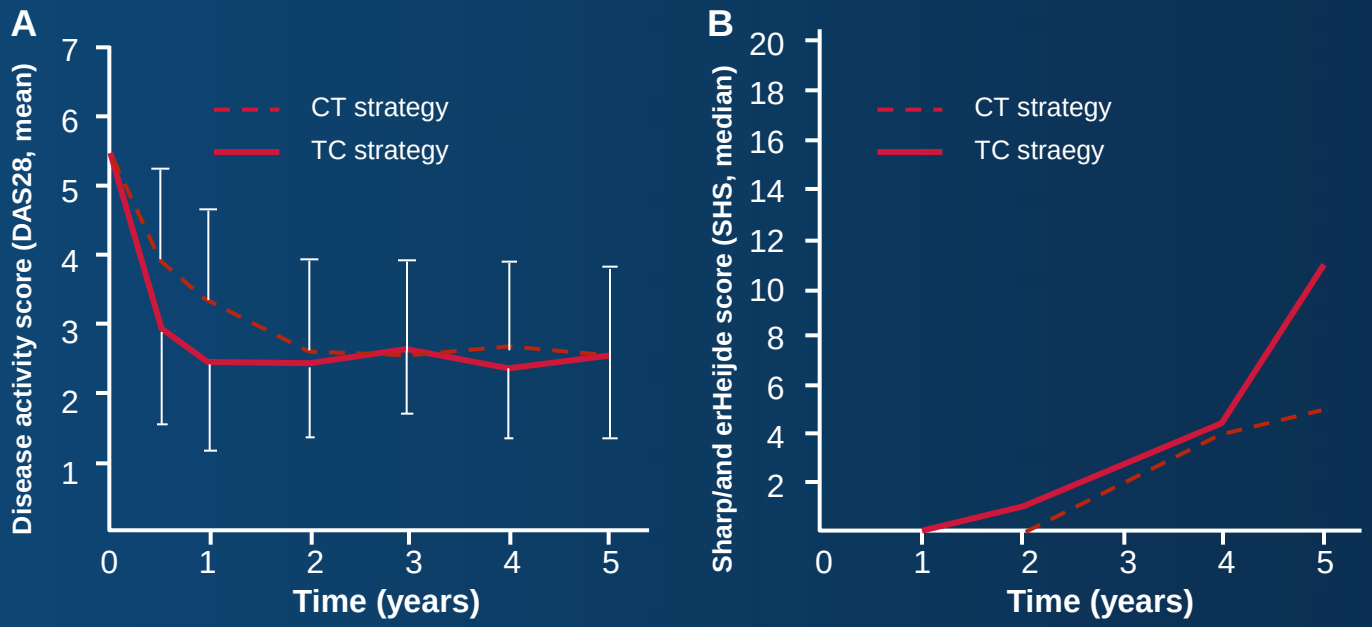
- 698 RA patients consecutively enrolled
- 527 remained at the 8-year follow-up visit.
- Sustained remission : DAS28 Cr (14%), ACR/Boolean 3%, SDAI 5% (9% & 8% if exclude Pt Global)

	Number (%) of patients in remission at all four, three, two, one or no visits				
	Sustained remission	Intermittent remission			Never remission
	All four visits	Three	Two	One	No visit
DAS28 Cr	69 (14)	76 (16)	81 (17)	90 (19)	167 (35)
DAS28-3 Cr	60 (12)	75 (15)	88 (17)	89 (18)	189 (38)
Boolean Cr	14 (3)	32 (6)	62 (11)	86 (17)	315 (62)
Boolean-3 Cr	45 (9)	51 (10)	90 (18)	115 (23)	199 (40)
SDAI Cr	22 (5)	34 (8)	67 (16)	56 (13)	245 (58)
SDAI-4 Cr	39 (8)	61 (13)	104 (22)	87 (18)	186 (39)

Svensson. BMJ Open 2013;3:e003554

Difference in Disease Activity Between Treatment Strategies Absent After 5 Years

- 5 years of data available for 205/299 patients
- No longer any significant difference for clinical and radiographic outcomes between treatment strategies applied during the first 2 years



- This may be because the TC strategy was abandoned for free medication after the 2-year trial

Bakker MF et al. Ann Rheum Dis 2011;70:1099-1103.

Early Response to Treatment: Independent Predictor of 5-year Outcome

- In multiple regression analyses, early response was significantly related to 5-year DAS28
  - The explained variance (R^2) of the model increased from 0.037 to 0.091 when including early response
  - Irrespective of treatment strategy

Multiple Regression Analysis with Disease Activity Score (DAS28) at 5 years of Treatment as Dependent Outcome

Item	B	95% CI	Standardised β	p value	R^2
Intercept	1.709	0.517 to 2.901		0.005	
Age	0.006	-0.007 to 0.018	0.066	0.384	0.001
Gender	0.347	-0.031 to 0.725	0.139	0.071	0.017
Treatment Strategy	0.174	-0.172 to 0.519	0.076	0.323	0.017
Rheumatoid factor positive	0.283	-0.083 to 0.649	0.113	0.128	0.036
Baseline disease activity	0.042	-0.126 to 0.211	0.039	0.622	0.038
EULAR good-response*	-0.752	-1.221 to -0.284	-0.313	0.002	
EULAR moderate-response*	-0.427	-0.877 to 0.023	-0.184	0.063	0.091

*Early EULAR non-response used as reference category. Age, gender and treatment strategy were used as covariates. R^2 = explained variance. The R^2 is shown for every extra variable included in the model.

DAS=disease activity score in 28 joints

Bakker MF et al. Ann Rheum Dis 2011;70:1099-1103.

Early Response to Treatment: Independent Predictor of 5-year Outcome (cont'd)

- In multiple regression analyses, early response was significantly related to the mean yearly radiographic progression rate
  - The explained variance (R^2) of the model increased from 0.208 to 0.242 when including early response
  - Irrespective of treatment strategy

Multiple Regression Analysis with Mean Yearly Radiographic Progression Rate after 5 years of Treatment as Dependent Outcome

Item	B	95% CI	Standardised B	p value	R2
Intercept	0.968	0.290 to 1.645			
Age	-0.001	-0.010 to 0.007	-0.020	0.773	0.000
Gender	-0.123	-0.370 to 0.124	-0.068	0.328	0.008
Treatment Strategy	0.171	-0.062 to 0.404	0.102	0.149	0.013
Rheumatoid factor positive	0.345	0.105 to 0.603	0.193	0.006	0.055
Baseline disease activity	0.070	0.044 to 0.095	0.365	0.000	0.200
EULAR good-response*	-0.427	-0.740 to -0.114	-0.246	0.008	
EULAR moderate-response*	-0.091	-0.329 to 0.210	-0.054	0.552	0.242

*Early EULAR non-response used as reference category. Age, gender and treatment strategy were used as covariates. R2 = explained variance. The R2 is shown for every extra variable included in the model.

Bakker MF et al. *Ann Rheum Dis* 2011;70:1099-1103.

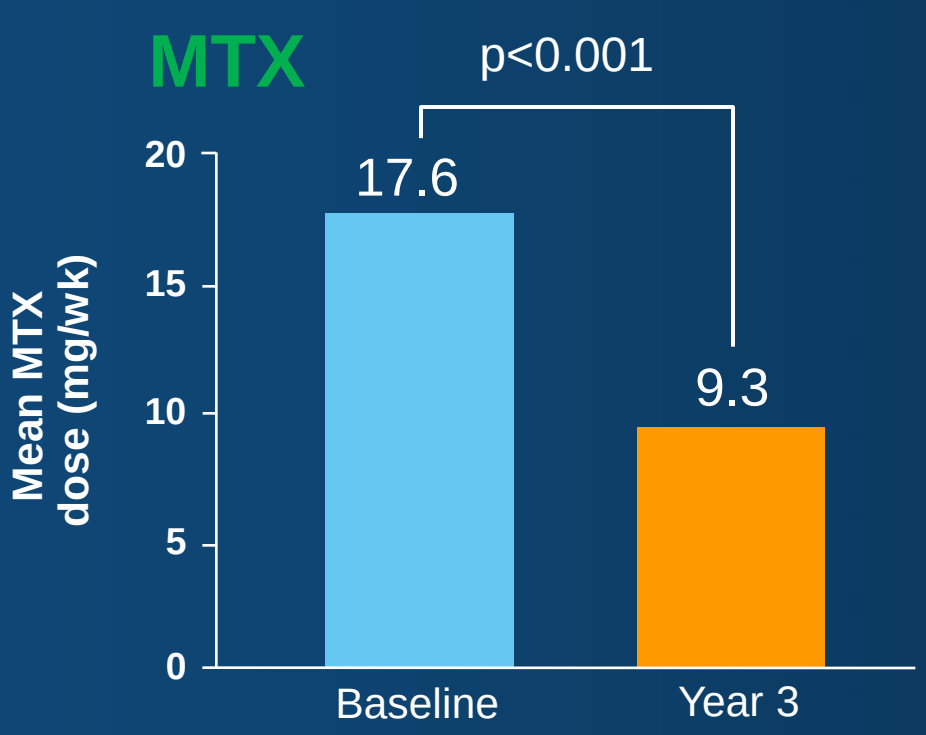
Remission in Rheumatoid Arthritis

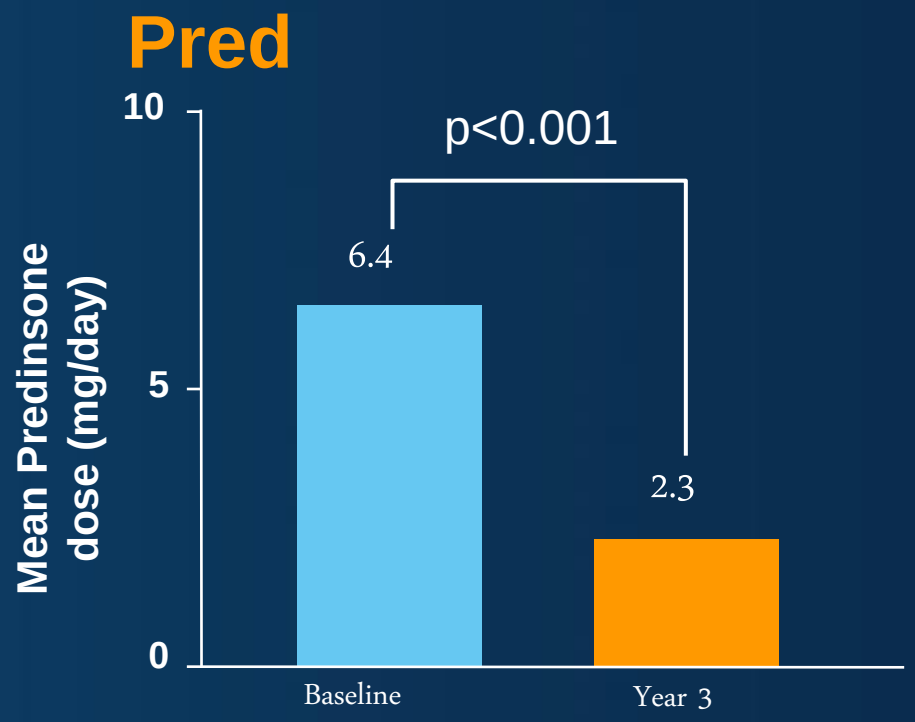
- High >50% in undifferentiated IA, Low in RA
- Prebiologic era: estimated to < 10%
- Success related to how fast & how deep
- Shorter time-to-remission related to sustainability of remission
- Duration in remission; predicts long-term remission

Schipper LG. Arthritis Res Ther. 2010; 12(3): R97
Navarro-Millan. Semin Arthritis Rheum. Oct 2013; 43(2): 137–143..

So Why Would We Want to Take Away Rx

Withdrawal of Methotrexate and Prednisone Change at 3 Years





	Methotrexate	Prednisone
Increased	3%	3%
Decreased or D/C	68%	85%
Discontinued	39%	59%

BeST Trial

- Group IV: MTX + Infliximab
  - Mandated cessation of infliximab if remission was achieved

Van der Biljil AE et al; *Arthritis Rheum* 2007 Jul;56(7):2129-34

Step-Down, Treatment Holidays, WD?

- Trials that examine withdrawal after Remission
  - 13 reports from 10 studies (for early RA (≤2 years).
    - TNF20
    - BeSt
    - OPITMA
    - HIT-HARD
    - IMPROVED
    - PRIZE
    - IDEA
    - EMPIRE
    - tREACH
    - AVERT
- 61.5% were published in 2013 or 2014

Hirata S. Expert Rev Clin Pharmacol 2014 Nov 25:1-8. [Epub]

OPTIMA: Early RA

- MTX naïve, early RA (<1yr)→ MTX + ADA vs MTX
- For those achieving LDA - compare 78-wk outcome
  - Continued treatment with ADA + MTX (maintenance)
  - ADA W/D → continue w/ PBO + MTX (step down)
- In those who failed to meet LDA with PBO + MTX assess the impact of adding ADA (step up)

OPTIMA = Optimal Protocol for Methotrexate and Adalimumab Combination Therapy in Early Rheumatoid Arthritis; ADA = adalimumab; PBO = placebo; LDA = low disease activity.

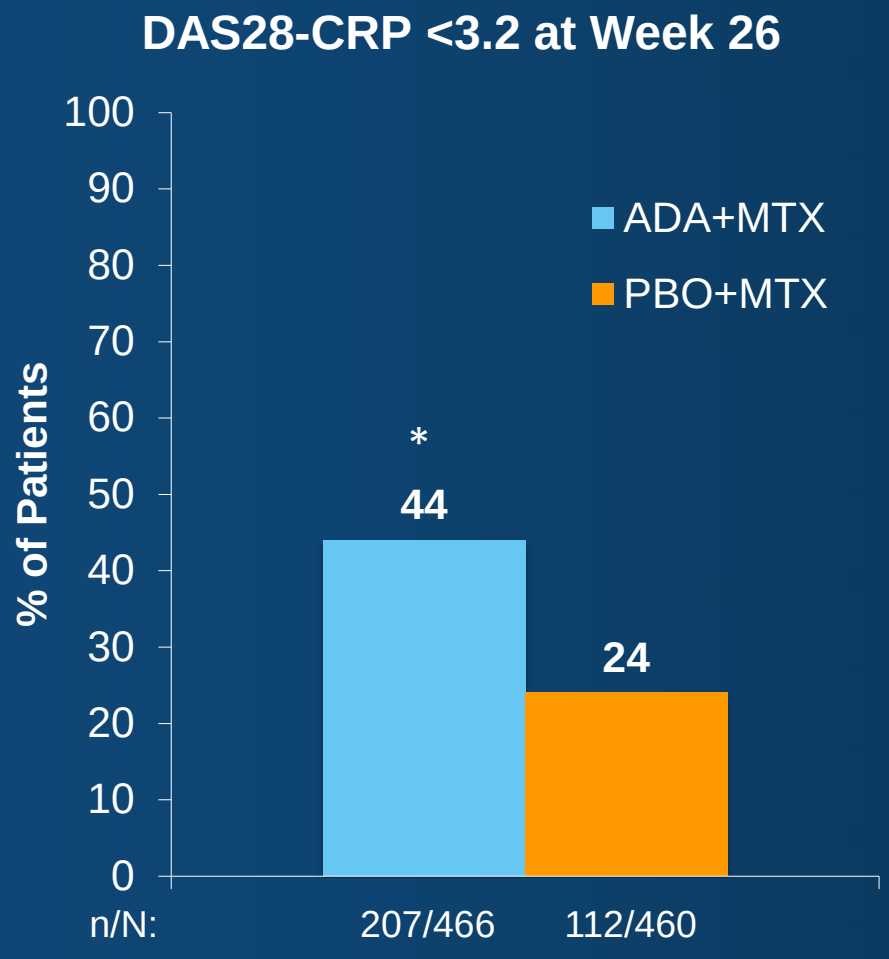
Emery P, et al. Ann Rheum Dis. 2011;70(Suppl 3):262.

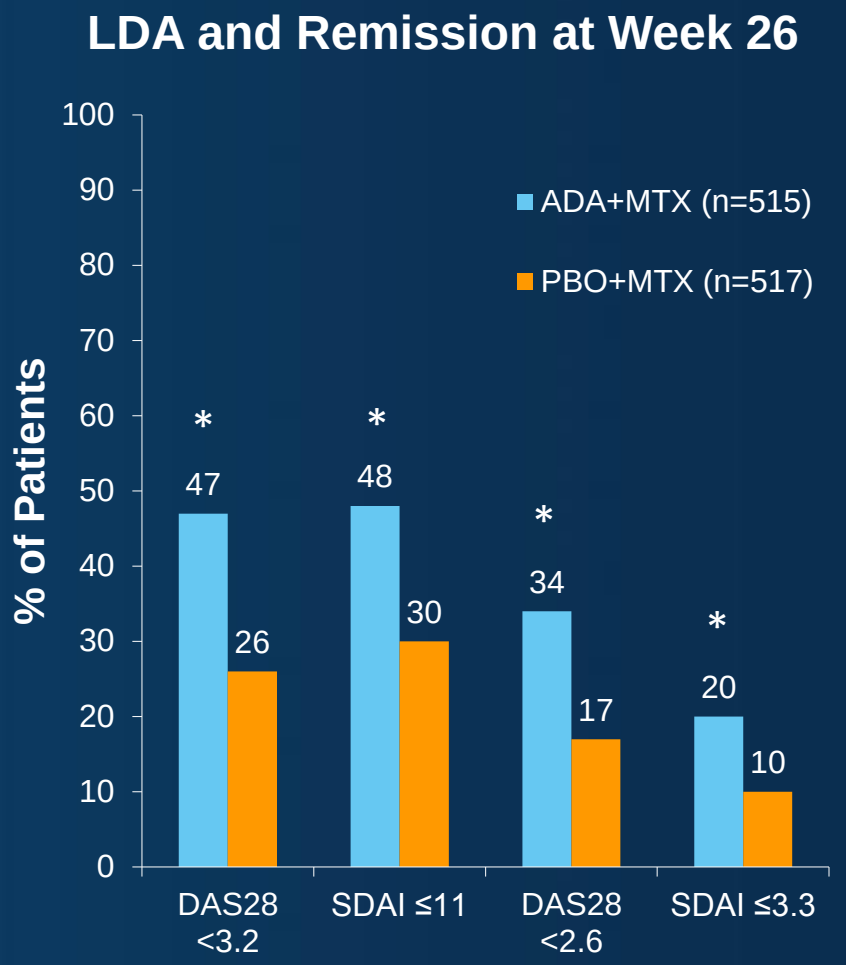
OPTIMA: Conclusions

- Compared with MTX, ADA + MTX achieved approx 2-times more stable LDA at weeks 22 and 26 (data not shown) and patients with sustained LDA Rx with ADA + MTX demonstrated higher levels (ACR70) of disease control at week 78
- Maintenance of LDA after induction was greater in the ADA +MTX maintenance group but MTX maintenance group response reasonable (ACR20)
- DNS: X-ray NON-progression at week 78
  - 89% Sustained ADA+MTX
  - 80% MTX +PB (ADA withdrawal grp)

Emery P, et al. *Ann Rheum Dis.* 2011;70(Suppl 3):262.

OPTIMA Trial: 26 Week Results





ADA=adalimumab; LDA=low disease activity; MTX=methotrexate

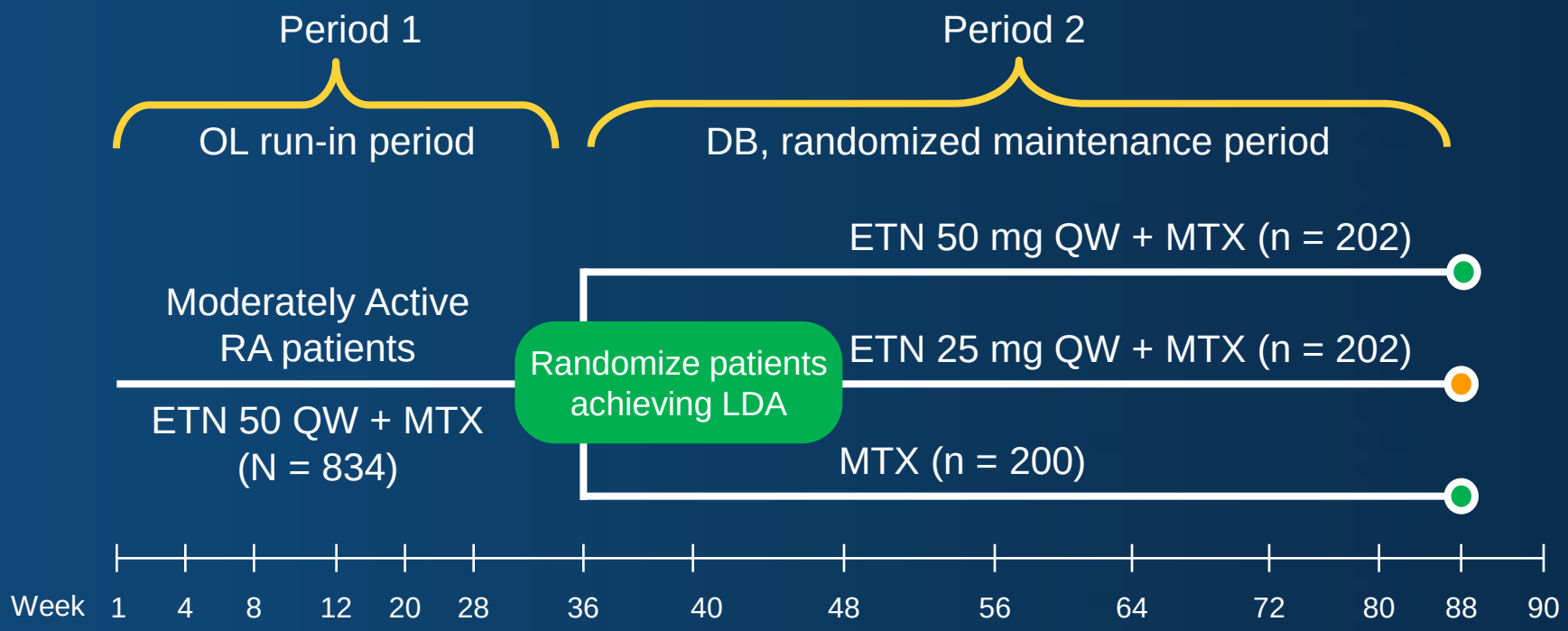
Kavanaugh A et al. Ann Rheum Dis. 2013;72:64-71.

PRESERVE: Established RA

- Methotrexate (MTX) + Etanercept (ETN) x 9 mos: those achieving LDAs:
  1) Continue same
  2) Reduce ETN 25/wk w/ MTX
  3) Stop ETN (PBO+MTX)
- Primary: Compare efficacy of continuing ETN 50 mg QW + MTX with that of MTX alone at week 88 in subjects with moderately active RA, who achieved LDA or remission after 36 weeks on OL ETN 50 mg + MTX
- Conditional primary: to compare efficacy of ETN 25 mg QW + MTX with that of MTX monotherapy as maintenance therapy

Smolen JS, et al. Lancet 2013;381:918-29

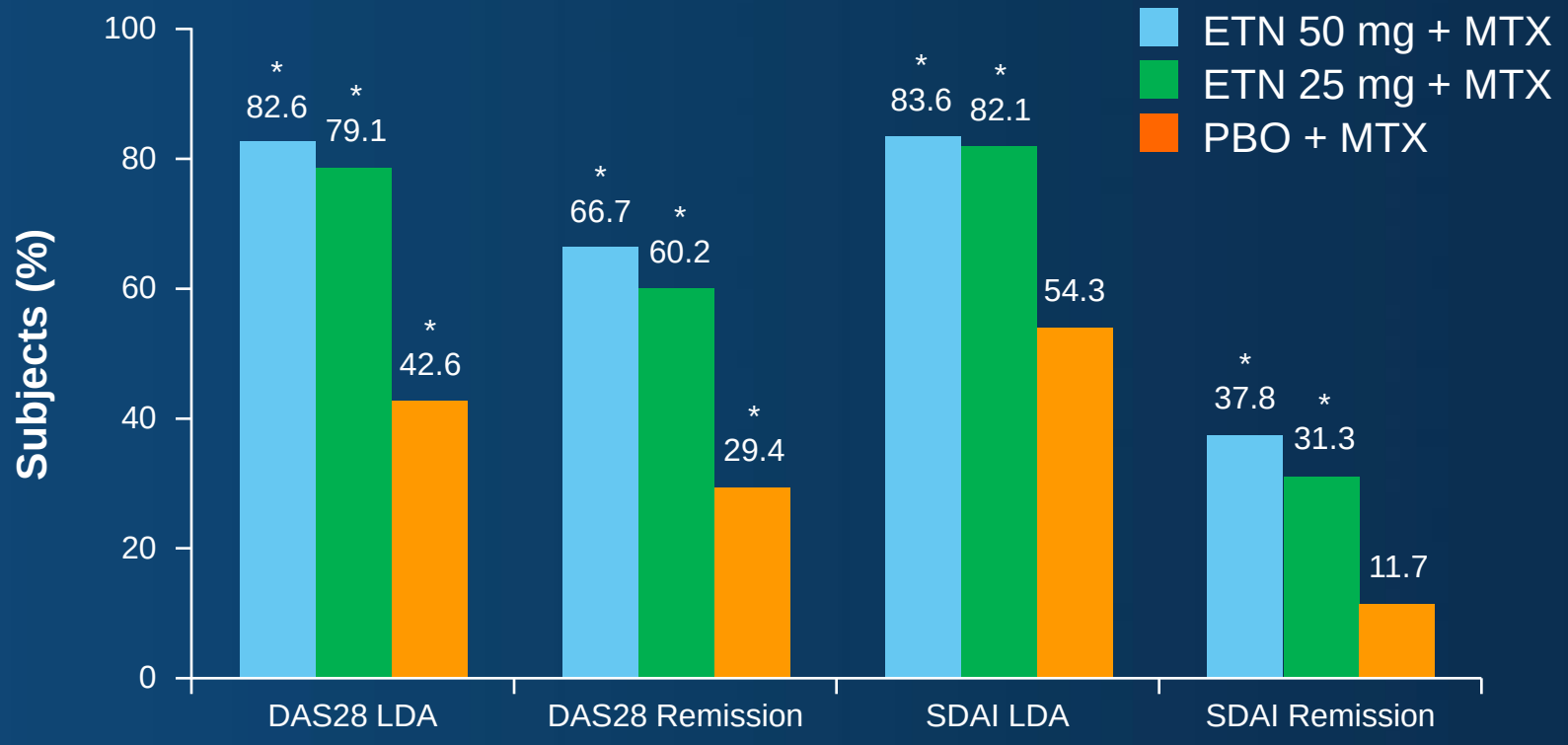
PRESERVE: Study Design



- X-rays at week 1, week 36, and week 88
- Week 90: follow-up phone call to assess new and ongoing adverse events

Smolen JS, et al. Lancet 2013;381:918-29

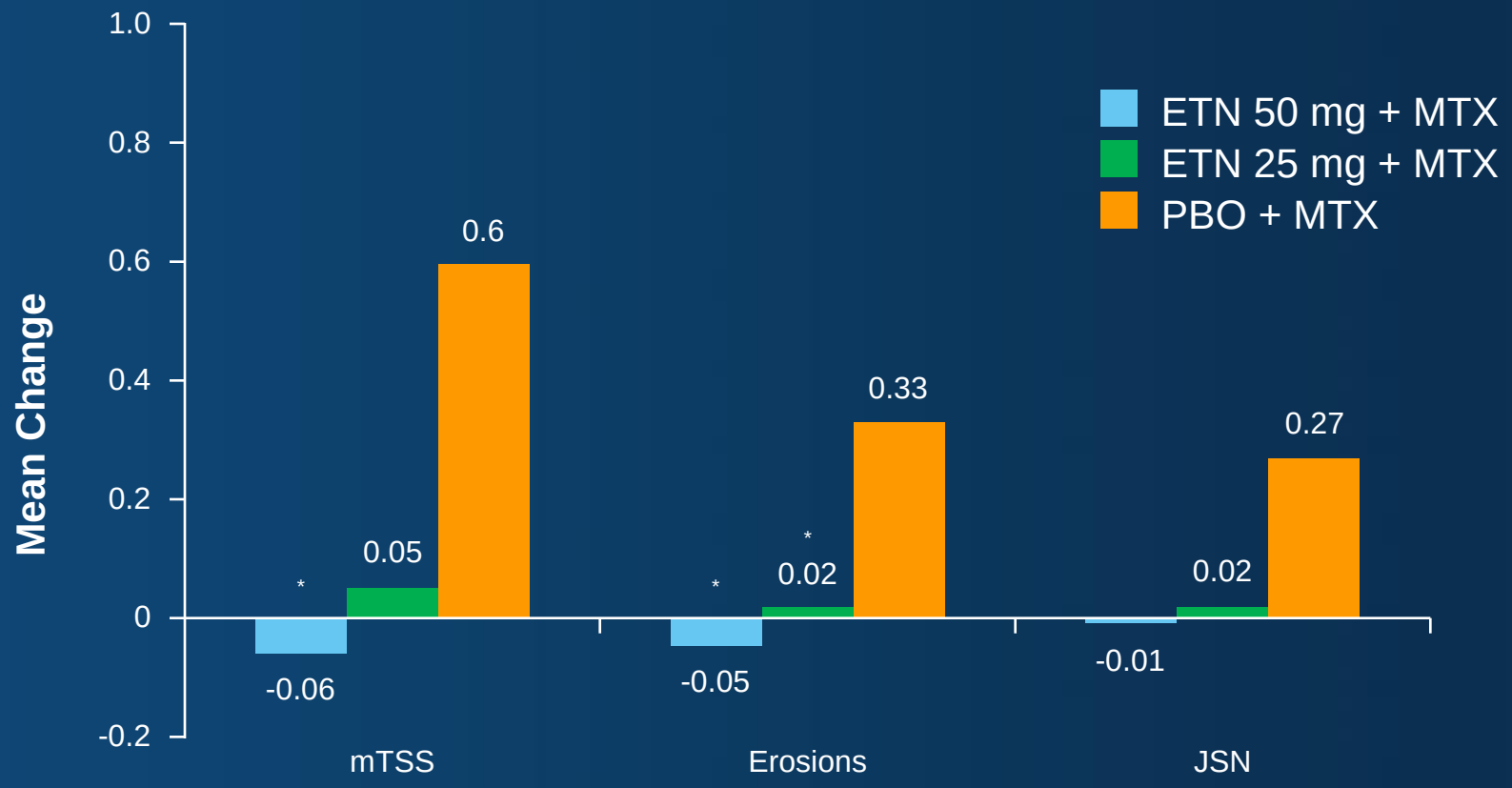
Proportion of Patients Maintaining Response at Week 88



- From P2 baseline (week 36) to week 88; DAS28 LDA, LOE; other efficacy endpoints, LOCF.
  *P< 0.0001, ETN 50 mg/25 mg + MTX vs PBO + MTX,

Smolen JS, et al. Lancet 2013;381:918-29

Radiographic Outcomes from Week 36-88



- From P2 baseline (week 36) to week 88; rITT, observed cases.
  *P<.05, ETN 50 mg/25 mg + MTX vs PBO + MTX, from ANCOVA model..

Smolen JS, et al. Lancet 2013;381:918-29

PRESERVE: Conclusions

- In patients achieving LDAS or remission,
  - ETN 50 and 25 mg + MTX achieved better sustained DAS28, LDAS and remission at week 88 compared to MTX + placebo
- ETN 25 mg and 50 mg + MTX achieved better radiographic protection compared to MTX + placebo
- You can lower, but not stop, the ETN

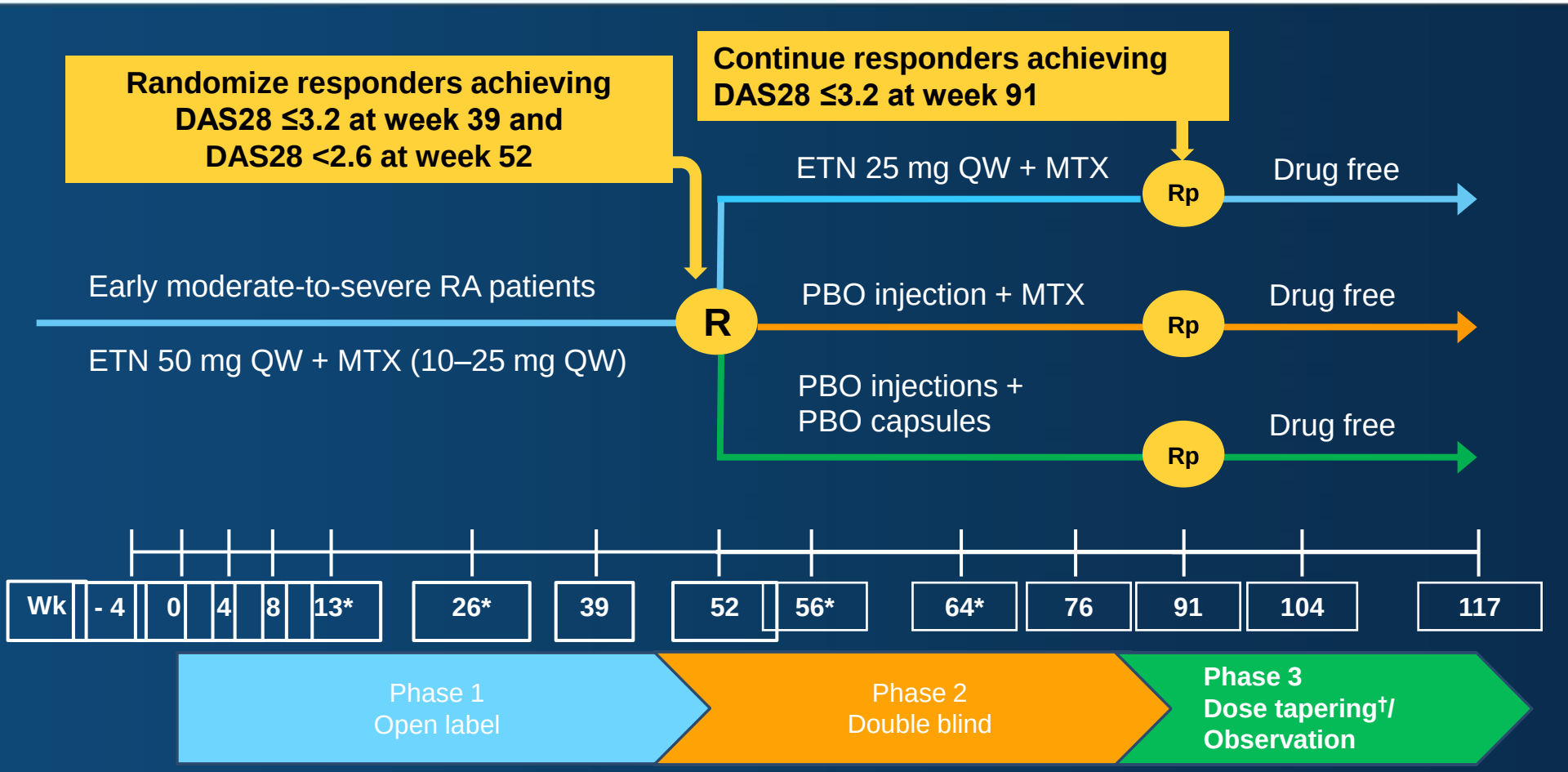
Smolen JS, et al. Lancet 2013;381:918-29

PRIZE Study: Objectives

- Purpose:
  - Phase 1: To evaluate efficacy & safety of etanercept + methotrexate (ETN+MTX) treatment of MTX- and biologic-naïve patients with active (DAS28 >3.2) early RA (□12 mos. since symptom onset)
  - Phase 2: To assess whether efficacy can be maintained with reduced-dose or biologic-free therapy.
  - Phase 3: To assess effect of subsequent withdrawal of drug therapy.

Emery P, et al. Arthritis Rheum. 2013;65 Suppl 10:2689.

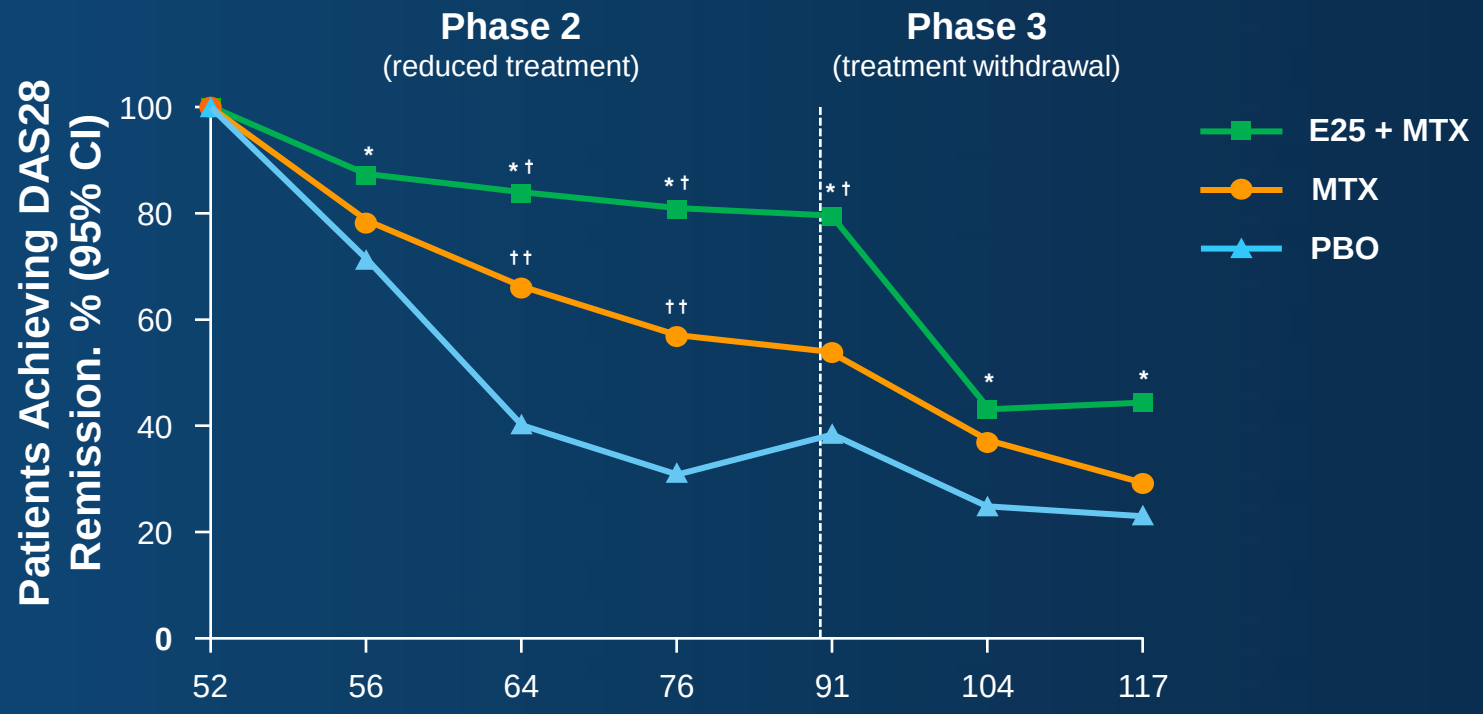
PRIZE Study Design: Overview of Phases 1□3



*Patients who did not achieve LDA at these time points were given corticosteroid boosts. †Over 2–4 weeks.
PBO = placebo; QW = once weekly; R = randomize; Rp = responders (DAS28 ≤3.2).

Emery P, et al. *Arthritis Rheum*. 2013;65 Suppl 10:2689.

PRIZE: DAS28 Remission Wk 52 to Wk 117 (LOCF)



Number							
E25 + MTX	63	55	53	51	50	27	28
MTX	65	51	43	37	35	24	19
Placebo	64	45	26	20	25	16	15

*p<.001 Wk 64, 76, 91; p<.05 Wk 56, 104, 117 for E25 vs. PBO; †p<.05 Wk 64, 76, 91 for ETN vs. MTX; ††p<.05 Wk 64, 76 for MTX vs PBO. n = number of responders at each time point.

Emery P, et al. Arthritis Rheum. 2012;64 Suppl 10:2549; Emery P, et al. Ann Rheum Dis. 2013;72 (Suppl3):399; Emery P, et al. Arthritis Rheum. 2013;65 Suppl 10:2689.

PRIZE: Conclusions

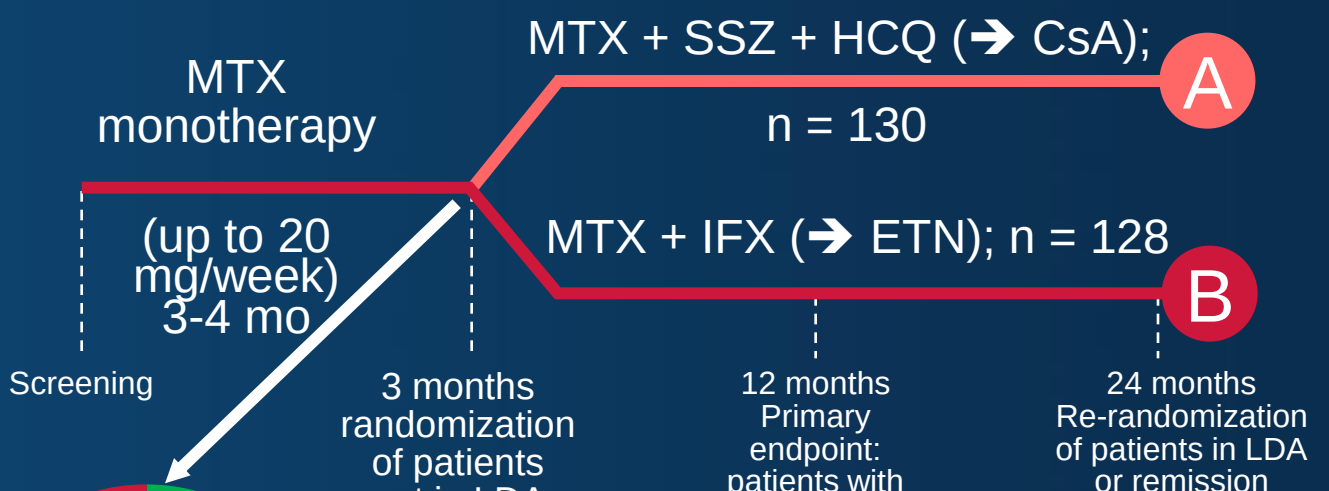
- Randomization of early RA patients in DAS28 remission to:
  - Reduced ETN dose (in Phase 2) resulted in modest loss of efficacy
  - Withdrawal of ETN (in Phase 2 or Phase 3) or of MTX (in Phase 3) resulted in steep declines in outcomes
- Cannot withdraw DMARD therapy, even in early RA, & maintain clinical response

Emery P, et al. *Arthritis Rheum*. 2013;65 Suppl 10:2689.

SWEFOT: Triple Therapy vs MTX/TNFi

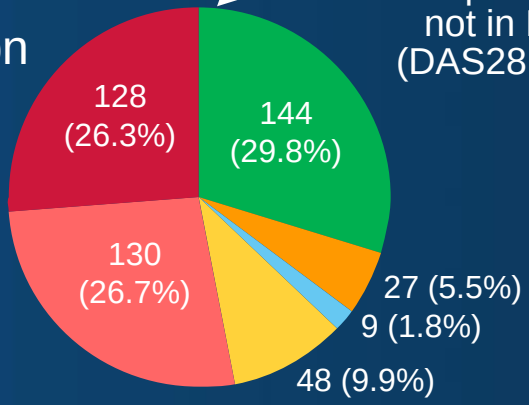
Early RA; Symptoms <1 year No other DMARD, DAS28 >3.2
N = 487

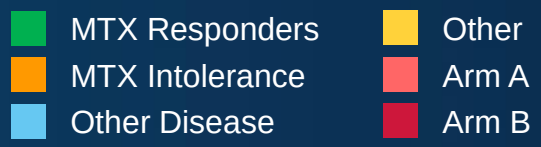
Mean age 52; Symptom duration 6.3 months; 67% RF+; DAS28 5.95;



Patient Disposition

- Randomized, not blinded





- Conclusion: 30% patients responded to initial 3- to 4-month MTX monotherapy (16% in remission)

van Vollenhoven RF, et al. Lancet. 2009;374(9688):459-466. van Vollenhoven RF, et al. Presented at: ACR 2009 Annual Scientific Meeting; October 17-21, 2009; Philadelphia, PA; Abstract 1010.

Tough Enough?
Who's the UnderTreater or OverTreater

The UNDERTREATER	The OVERTREATER
Most Pts on Monotherapy	Everyone on MTX+DMARD
Incremental dosing	Highest dose 1st
Focused exam; Gestalt Rx	Measure and Treat to Target
LDAs is the goal	Remission or bust
Most Pts on MTX	Everyone on MTX

Under-Treatment or Just-Right ?

You won’t know until you’ve succeeded or failed

Justifying Over-Treatment

- You really don’t know who the bad ones are
- Evidence that Under-treatment is prevalent
- SAFE Rx to reduce damage and mortality
  - Methotrexate, TNFi
- X-ray outcomes with aggressive biologic Rx of non-responders
- So which is it?
  - First do no harm
  - The path to remission need not involve harm

Which Best Describes Your Philosophy in Treating Active RF+ Rheumatoid Arthritis Patients?

Answer Options	Response Percent
Therapy should be tailored to disease activity	**27.1%**
Methotrexate is the dominant cornerstone of RA care	**25.5%**
I use aggressive combo DMARDs in most patients	**19.9%**
TNF inhibitors give the greatest responses in the most number of patients	**26.8%**
Steroids and DMARDs work as well as any other regimen	**0.5%**
NSAIDs, analgesics and prednisone are sufficient for many patients	**0.0%**
Hydroxychloroquine is safe and effective in most	**0.3%**

N=377

Who R U?

MTX Centric 25%	**Adaptive Rx 27%**
Aggressive Traditional 20%	**Aggressive Novel 27%**

Over Treatment

THE DOWN-SIDE

NO BENEFIT/HARM ONLY

- Antinuclear antibodies + fibromyalgia = SLE?
- B27- Seronegative SpA?
- Lyme disease in Texas
- Asymptomatic hyperuricemia

THE UPSIDE

CLEAR BENEFIT/ NO HARM

- PROMPT
- TICORA
- Induction Regimen
- ASPIRE, Premire, BeST4
- SWEFOT, TEAR, COMET