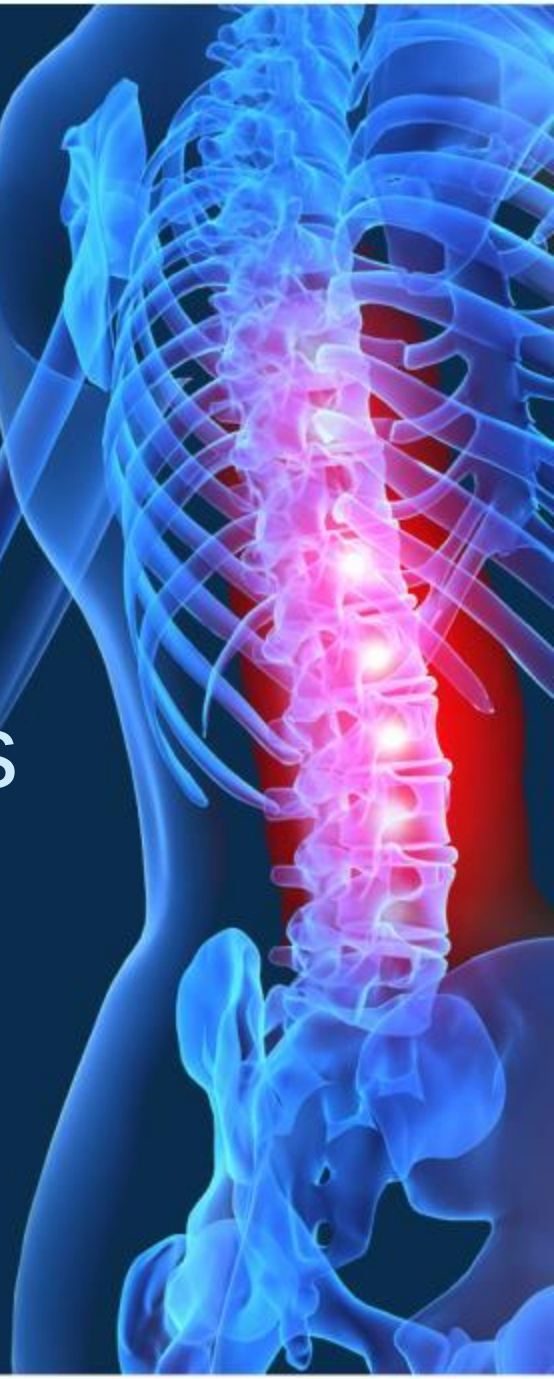
Annual Rheumatology & Therapeutics Review for Organizations & Societies



Comparative Effectiveness Studies of Biologics

Learning Objectives

- Understand the motivation for comparative effectiveness research (CER) studies in rheumatoid arthritis
- Compare and contrast different types of study designs useful for CER
- Evaluate results from head to head randomized controlled trials of biologics agents

What is Comparative Effectiveness?

- "Comparing treatment options for different health conditions"
  - "Provides comparisons of drugs, medical devices, tests, surgeries, or ways to deliver health care so that patients and their families understand what treatments work best and how their risks compare."
  - "Improve[s] health care quality by providing patients and physicians with state-of-the-science information on which medical treatments work best for a given condition."
  - Based on this framework, a comparison to placebo (typical for a phase 3 registration trial) is not relevant

Comparative Effectiveness: Comparing treatment options for different health conditions. October 2012. Agency for Healthcare Research and Quality, Rockville, MD. http://www.ahrq.gov/cpi/portfolios/comparative-effectiveness/index.html

Types of CER Studies

- Randomized controlled trial
- Observational study
  - Registries
  - Health plan data
- Meta-analysis and variants
  - Network meta-analysis
  - Indirect comparisons
  - Mixed treatment comparisons

Comparative Effectiveness Studies of Biologics in RA

- Analyses of prospective, observational cohort studies comparing response to switching from TNF inhibitor (TNFi) to rituximab or to alternative TNFi in RA patients who had an inadequate response to ≥ 1 TNFi
  - Finckh et al.
  - SWITCH-RA
  - Corrona Abatacept comparison
- Randomized, double-blind clinical trial comparing efficacy of abatacept & infliximab indirectly, by comparing each to placebo in parallel, and safety of each directly in RA patients who had an inadequate response to MTX (ATTEST)
- Head-to-head studies of biologic agents in RA
  - AMPLE: abatacept + MTX vs. adalimumab + MTX in RA patients who had an inadequate response to MTX
  - ADACTA: tocilizumab monotherapy vs. adalimumab monotherapy in RA patients who had an inadequate response to MTX or were intolerant of MTX

Finckh A, et al. Arthritis Rheum. 2007; 56: 1417-1423; Rubbert-Roth A, et al. 2012 ACR Annual Meeting, Abstract 467;
Schiff M et al. Ann Rheum Dis. 2008; 67: 1096-1103; Weinblatt ME, et al. Arthritis Rheum. 2013; 65: 28-38;
Gabay C, et al. EULAR 2012. Ann Rheum Dis. 2012;71(Suppl3):152. Abstract LB003; Kavanaugh A, et al. 2012 ACR Annual Meeting, Abstract 772.

Switching from TNF Inhibitor to Rituximab or Alternative TNF Antagonist

- First study comparing effectiveness of two therapeutic strategies in RA patients who had an inadequate response to ≥ 1 anti-TNF agent
- Prospective, observational longitudinal cohort study of 116 RA patients enrolled in Swiss Clinical Quality Management Program for RA (SCOM-RA) who had an inadequate response to ≥ 1 TNF antagonist
  - 50 (43%) received rituximab 1000 mg i.v. × 2 + i.v. glucocorticoids
  - 66 (57%) received a 2nd or 3rd TNF antagonist
    - 49% treated with adalimumab 40 mg subcut every other week
    - 27% treated with etanercept 50 mg subcut weekly
    - 24% treated with infliximab i.v. (starting at 3 mg/kg)
- Treatment decisions made by the treating physician (not randomized)

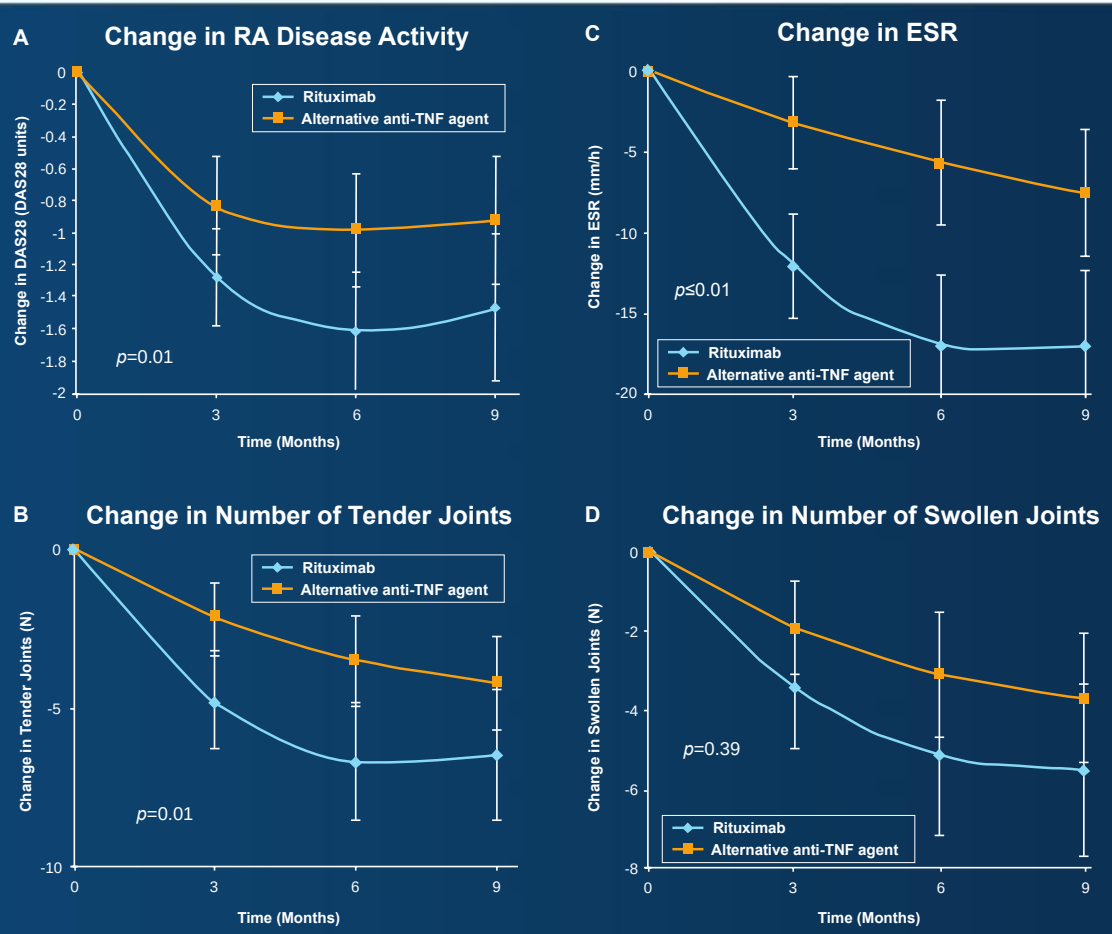
Finckh A, et al. *Arthritis Rheum*. 2007; 56: 1417-1423.

Switching from TNF Antagonist to Rituximab or Alternative TNF Antagonist

Baseline Characteristic	Rituximab (n = 50)	Alternative anti-TNF agent (n = 66)	P
Rheumatoid factor positivity	90%	92%	0.65
Disease duration at inclusion, median (IQR) yrs	10 (6–18)	9 (5–16)	0.39
DAS28, mean (95% CI)	5.43 (4.99–5.87)	5.01 (4.70–5.32)	0.11
ESR, mm/hr	39 (31–46)	34 (28–40)	0.31
Tender joint count	11 (8–13)	10 (8–11)	0.44
Swollen joint count	10 (8–13)	8 (6–10)	0.17
Radiographic damage (Ratingern score), median (IQR)	8 (6–17)	8 (3–31)	0.90
HAQ score, median (IQR)	1.4 (0.9–2.0)	1.6 (1.1–2.1)	0.16
Concomitant methotrexate	52%	39%	0.18
Concomitant leflunomide	16%	14%	0.72
Concomitant treatment with other DMARD	10%	9%	0.87
No concomitant DMARD	28%	39%	0.20
Concomitant low-dose oral glucocorticoid treatment	58	55%	0.71
Previous anti-TNF agents, median (IQR)	2 (1–2)	1 (1–2)	0.001
Prior anti-TNF treatment for ≤6 months	16%	15%	
Prior anti-TNF treatment for >6 months	84%	85%	0.43

Finckh A, et al. *Arthritis Rheum*. 2007; 56: 1417-1423.

Switching from TNF Antagonist to Rituximab or Alternative TNF Antagonist



- Greater improvement in DAS 28, TJC, & ESR at 6 months with rituximab than with an alternative TNF antagonist

Finckh A, et al. *Arthritis Rheum*. 2007; 56: 1417-1423.

Switching from TNF Antagonist to Rituximab or Alternative TNF Antagonist

Safety

- Overall, no significant difference in tolerance between the 2 groups
- Patients receiving anti-TNF therapy reported more dermatologic complications (mainly injection site reactions [9 events vs. 1 event in a patient receiving rituximab, $P = 0.03$])
- Patients receiving rituximab reported more allergic complications (mild-to -moderate infusion reactions [3 events vs. none in patients receiving anti-TNF therapy; $P = 0.04$])
- Other side effects occurred with similar frequency in both groups

Finckh A, et al. *Arthritis Rheum*. 2007; 56: 1417-1423.

Switching from TNF Antagonist to Rituximab or Alternative TNF Antagonist

Conclusion

- RTX may be more effective than switching to an alternative anti-TNF agent for RA patients who experienced an inadequate response with ≥1 anti-TNF agent

Limitations

- Non-randomized assignment of treatment with RTX vs. an alternative anti-TNF agent
  - Could result in selection bias or confounding by indication
- However, patients receiving RTX had experienced an inadequate response with significantly more anti-TNF agents than patients receiving an alternative anti-TNF agent
  - May have had more aggressive disease, which would tend to bias results toward the null hypothesis

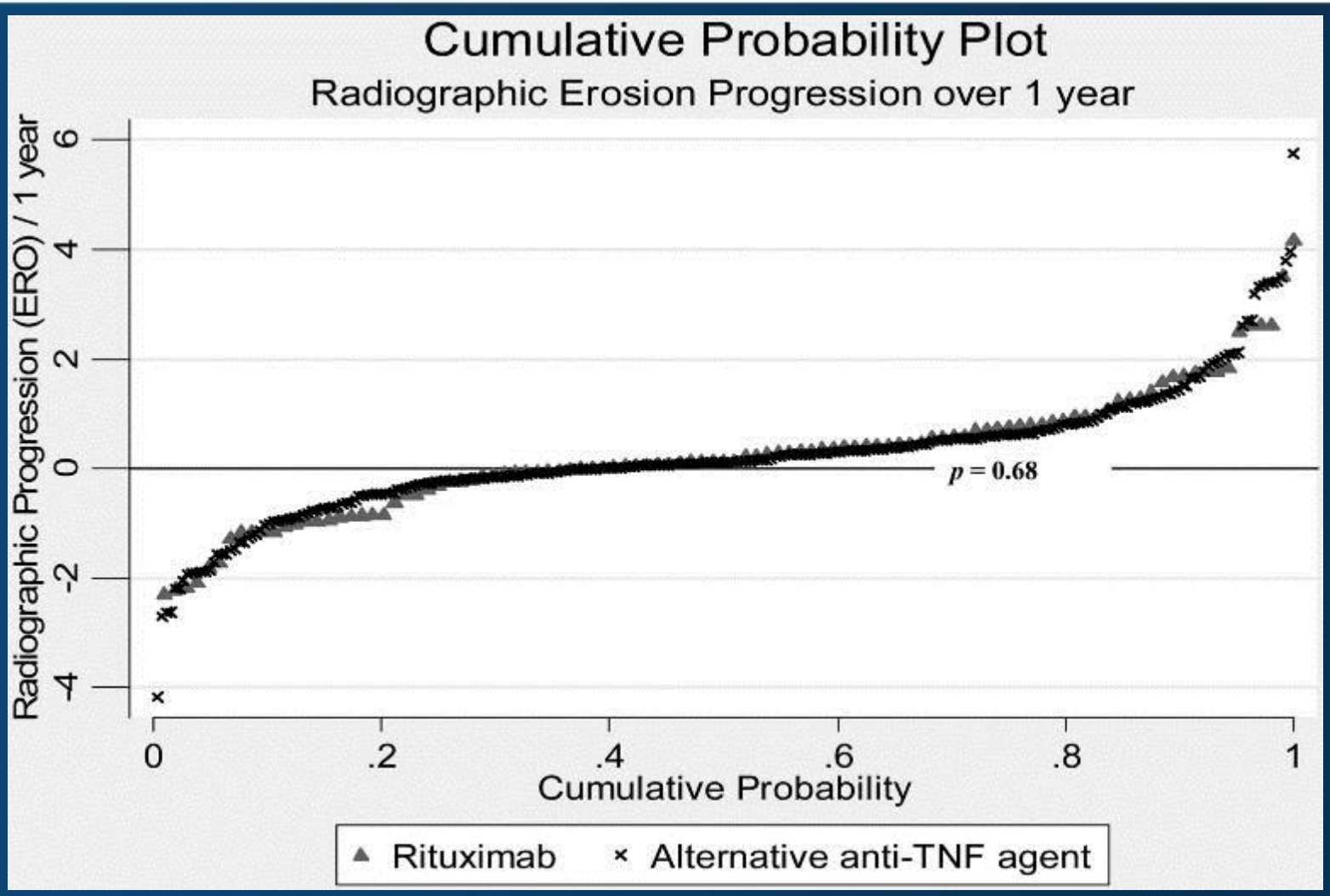
Finckh A, et al. *Arthritis Rheum*. 2007; 56: 1417-1423.

Switching from TNF Antagonist to Rituximab or Alternative TNF Antagonist: Structural Progression & Functional Disability

- Prospective, observational longitudinal cohort study of 650 RA patients enrolled in Swiss Clinical Quality Management Program for RA (SCOM-RA) who had an inadequate response to ≥ 1 TNF antagonist
- 371 of the 650 patients (57%) had subsequent radiographic assessments
  - 104 (28%) received rituximab 1000 mg i.v. × 2 + i.v. glucocorticoids
  - 267 (72%) received another TNF antagonist
- Median follow-up period: 2.6 years (IQR 1.6–3.6).
- **Primary endpoint:** Progression of radiographic erosion, as measured by change in Ratingen erosion scores from baseline
- **Secondary endpoint:** Evolution of functional disability, measured as change in the Health Assessment Questionnaire Disability Index (HAQ-DI) from baseline

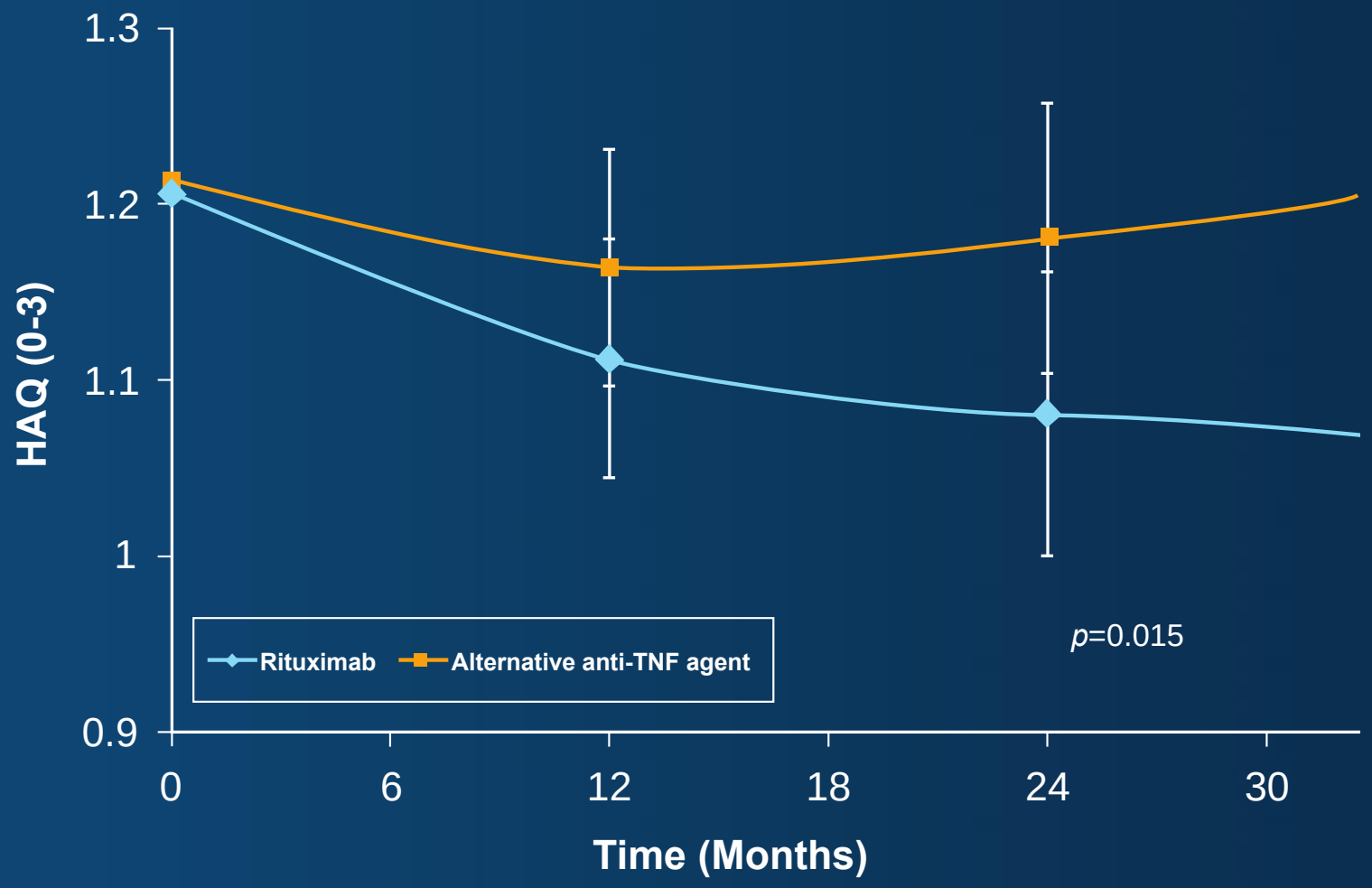
Finckh A, et al. *Ann Rheum Dis*. 2012; 71: 1680-1685.

Switching from TNF Antagonist to Rituximab or Alternative TNF Antagonist: Structural Progression



Finckh A, et al. *Ann Rheum Dis*. 2012; 71: 1680-1685.

Switching from TNF Antagonist to Rituximab or Alternative TNF Antagonist: Evolution of Functional Disability



Finckh A, et al. *Ann Rheum Dis*. 2012; 71: 1680-1685.

Switching from TNF Antagonist to Rituximab or Alternative TNF Antagonist: Structural Progression & Functional Disability

Conclusions

- No significant differences in rates of erosion progression between patients taking an alternative anti-TNF agent and patients taking RTX
- Longitudinal evolution of functional disability was statistically significantly better in RTX group, compared to alternative anti-TNF group (p=0.015)
  - Mean difference of 0.09 HAQ-DI units was far less than minimally clinically important difference, estimated to be at least 0.22 HAQ-DI units

Limitations

- Selection bias may arise because of non-random assignment to therapy
- Difficult to determine whether RTX & anti-TNF agents were used optimally
- Did not assess the relative benefit of RTX & anti-TNF agents on joint space narrowing or cartilage degradation

Finckh A, et al. *Ann Rheum Dis*. 2012; 71: 1680-1685.

SWITCH-RA: Rituximab vs. Alternative Anti-TNF Agent

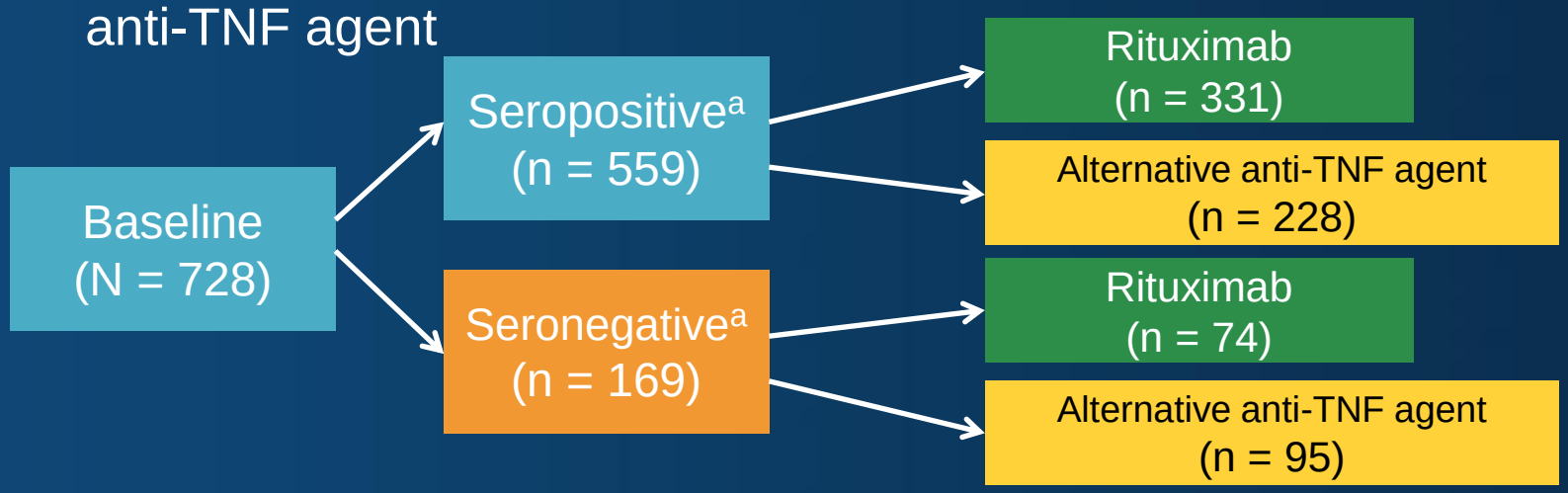
- Prospective, multicenter, observational cohort study to evaluate in routine clinical practice the relative effectiveness of RTX vs. a 2nd anti-TNF agent following an inadequate response (IR) to a single previous anti-TNF agent

- Primary endpoint: 6-month change from baseline in DAS28(3)-ESR

Rubbert-Roth A, et al. ARD Online, January, 2014; 10.1136/annrheumdis-2013-2039937.

SWITCH-RA: Rituximab vs. Alternative Anti-TNF Agent

- Patients with an inadequate response to a single previous anti-TNF agent



Baseline DAS28-3 (ESR) Scores, at Time of Switch	Rituximab	Alternative Anti-TNF Agent	*P*
Seropositive patients	5.2	4.8	.0001
Seronegative patients	5.3	4.7	.0019

[a]RF+ and/or anti-CCP+.

Rubbert-Roth A, et al. 2012 ACR Annual Meeting, Abstract 467.

SWITCH-RA: Rituximab vs. Alternative Anti-TNF Agent Changes in DAS28(3)-ESR at 6 months

	Seropositive patients* (n=559)			Seronegative patients† (n=169)		
LS mean (SE)	Rituximab	TNF Inhibitor	P-value	Rituximab	TNF Inhibitor	P-value
All patients	-1.6 (0.3)	-1.2 (0.3)	0.011	-1.3 (0.4)	-1.1 (0.4)	0.449
Inefficacy	-1.9 (0.3)	-1.5 (0.4)	0.021	-0.5 (0.6)	-0.2 (0.7)	0.472
Intolerance	-0.5 (0.5)	-0.5 (0.5)	0.997	-2.1 (1.2)	-1.9 (1.3)	0.815

- Following discontinuation of initial anti-TNF agent, seropositive patients with RA who switch to rituximab achieved significantly improved effectiveness over 6 months, in particular those interrupting therapy due to inefficacy, compared with patients switching to a 2nd anti-TNF agent
  - These differences were not evident in seronegative patients

*Seropositive patient numbers (all/inefficacy/intolerance): rituximab = 331/253/74; anti-TNF agent = 228/171/51.
†Seronegative patient numbers (all/inefficacy/intolerance): rituximab = 74/58/15; anti-TNF agent = 95/65/28.

Rubbert-Roth A, et al. 2012 ACR Annual Meeting, Abstract 467.

Corrona ABA study

- Please add figures 2 & 3 from ARD paper by Harrold et. al.

ATTEST: Abatacept or Infliximab vs. Placebo

- Randomized, double-blind, double-dummy, placebo- and active (infliximab)-controlled, 12-month trial of abatacept or infliximab in RA patients
  - Obtain relative efficacy and safety data on abatacept & infliximab in a single study during 6-month placebo-controlled phase
  - Directly compare safety profiles of abatacept & infliximab during continuation of active biologic treatment over 1 year
    - On day 198, placebo-treated patients were reallocated to abatacept (with blinding maintained).
    - Patients initially randomized to abatacept or infliximab continued their treatment.
- Patients with active RA (SJC ≥ 10, TJC ≥ 12, & CRP ≥ 10 mg/L) despite MTX ≥ 15 mg/wk for ≥ 3 months prior to randomization
  - Abatacept was dosed according to weight
  - Infliximab was dosed at 3 mg/kg for all patients
- Primary endpoint: Reduction in disease activity, measured by DAS28 (ESR) for abatacept vs. placebo at 6 months

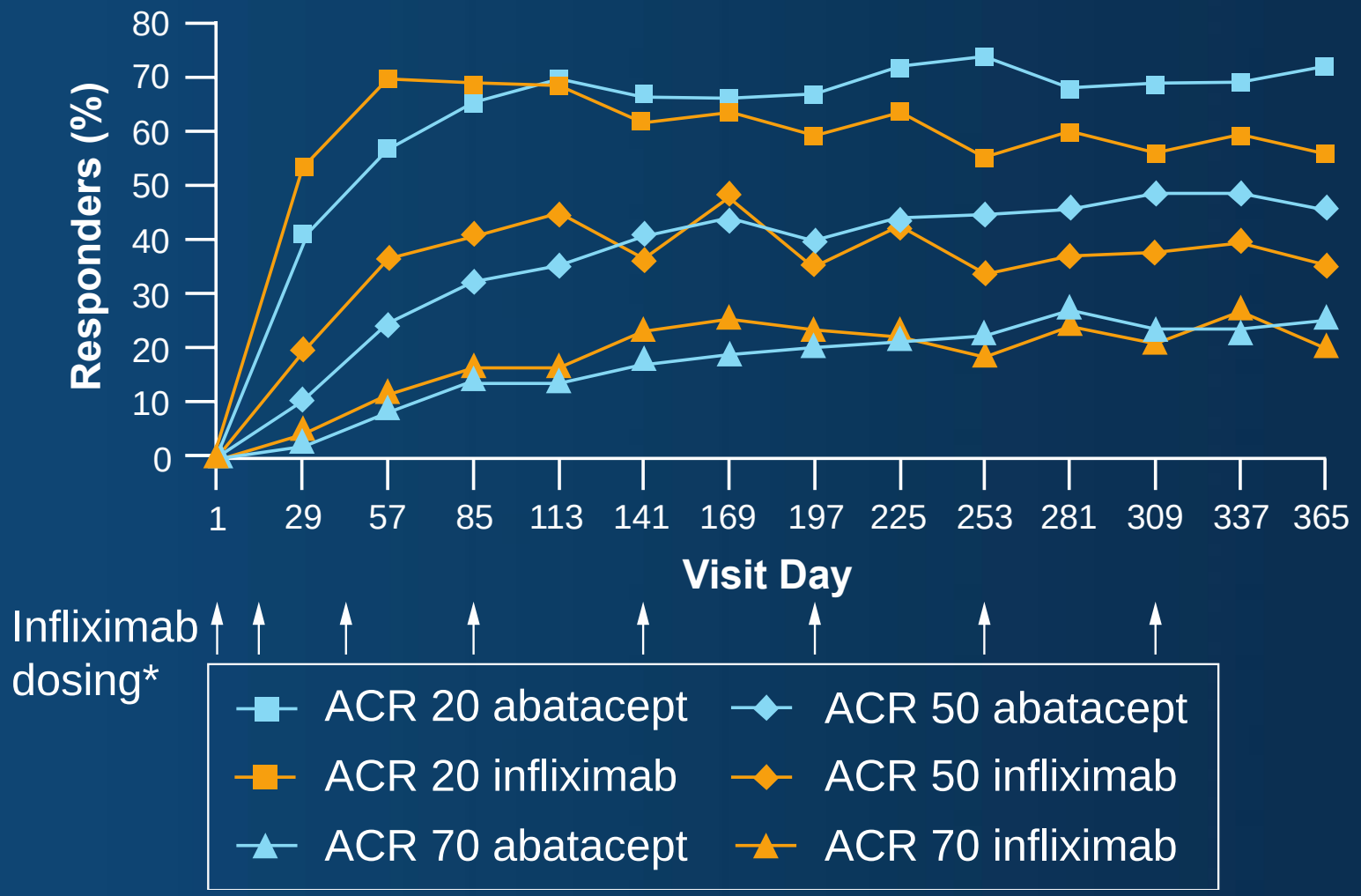
Schiff M et al. *Ann Rheum Dis* 2008; 67: 1096-1103.

ATTEST: Abatacept or Infliximab vs. Placebo

Baseline characteristic	Abatacept + MTX (n=156)	Placebo + MTX (n=110)	Infliximab + MTX (n=165)
Disease duration, years (SD)	7.9 (8.5)	8.4 (8.6)	7.3 (6.2)
Tender joints, n (SD)	31.6 (13.9)	30.3 (11.7)	31.7 (14.5)
Swollen joints, n (SD)	21.3 (8.6)	20.1 (7.0)	20.3 (8.0)
ESR, mm/h (SD)	49.4 (31.2)	47.0 (32.6)	47.8 (30.4)
CRP levels, mg/dl (SD)	3.1 (2.7)	2.7 (2.6)	3.3 (3.2)
DAS28 (ESR), n (SD)	6.9 (1.0)	6.8 (1.0)	6.8 (0.9)
HAQ-DI, 0–3 (SD)	1.8 (0.6)	1.8 (0.7)	1.7 (0.7)
Rheumatoid factor +, n (%)	136 (87.2)	85 (77.3)	140 (84.8)
Pts on concomitant medications, n (%)	156 (100)	110 (100)	165 (100)
Concomitant MTX, n (%)	156 (100)	110 (100)	164 (99.4)
Dose, mg/week (SD)	16.5 (3.7)	16.6 (3.7)	16.3 (3.6)
Duration, months (SD)	18.3 (20.0)	23.7 (25.6)	23.6 (26.8)
Concomitant corticosteroids, n (%)	118 (75.6)	77 (70.0)	118 (71.5)
Concomitant NSAIDs, n (%)	133 (85.3)	93 (84.5)	142 (86.1)

Schiff M et al. *Ann Rheum Dis* 2008; 67: 1096-1103.

ATTEST: Abatacept or Infliximab vs. Placebo
ACR Responses Over 1 Year



Schiff M et al. *Ann Rheum Dis* 2008; 67: 1096-1103.

ATTEST: Abatacept or Infliximab vs. Placebo

Safety Summary

	Days 1–197			Days 1–365	
	Abatacept + MTX (n=156)	Placebo + MTX (n=110)	Infliximab + MTX (n=165)	Abatacept + MTX (n=156)	Infliximab + MTX (n=165)
	n (%)*	n (%)*	n (%)*	n (%)*	n (%)*
Deaths	1 (0.6)	0	1 (0.6)	1 (0.6)	2 (1.2)
SAEs	8 (5.1)	13 (11.8)	19 (11.5)	15 (9.6)	30 (18.2)
Related SAEs	3 (1.9)	3 (2.7)	8 (4.8)	5 (3.2)	14 (8.5)
Discontinuations due to SAEs	2 (1.3)	0	4 (2.4)	4 (2.6)	6 (3.6)
AEs	129 (82.7)	92 (83.6)	140 (84.8)	139 (89.1)	154 (93.3)
Related AEs	64 (41.0)	46 (41.8)	74 (44.8)	72 (46.2)	96 (58.2)
Discontinuations due to AEs	3 (1.9)	1 (0.9)	8 (4.8)	5 (3.2)	12 (7.3)
Serious infections	2 (1.3)	3 (2.7)	7 (4.2)	3 (1.9)	14 (8.5)
Autoimmune symptoms and disorders	1 (0.6)	1 (0.9)	1 (0.6)	2 (1.3)	1 (0.6)
Malignant neoplasms	1 (0.6)	1 (0.9)	2 (1.2)	1 (0.6)	2 (1.2)

* ≥1 AE or SAE could be reported in each patient; percentages represent the proportion of patients who reported ≥1 event.

Schiff M et al. *Ann Rheum Dis* 2008; 67: 1096-1103.

ATTEST:
Abatacept or Infliximab vs. Placebo

Conclusions

- Abatacept & infliximab (3 mg/kg every 8 weeks) demonstrated similar efficacy
- Over 1 year, fewer SAEs, AEs, infections, and discontinuations due to AEs or SAEs were observed with abatacept than with infliximab

Limitations

- Abatacept & infliximab were not compared directly
- Abatacept was dosed as in clinical practice, but optimal doses of infliximab may not have been used (no dose escalation permitted)

Schiff M et al. *Ann Rheum Dis* 2008; 67: 1096-1103.

Head-to-Head Studies of Biologic Agents in RA

Study Name	Reference	Regimen
AMPLE	Weinblatt ME et al. Arthritis Rheum 2013; 65: 28-38.	Abatacept vs. adalimumab as part of MTX combination therapy
ADACTA	Gabay C et al. EULAR 2012. Abstract LB0003 & Kavanaugh A, et al. 2012 ACR Annual Meeting, Abstract 772.	Tocilizumab vs. adalimumab monotherapy

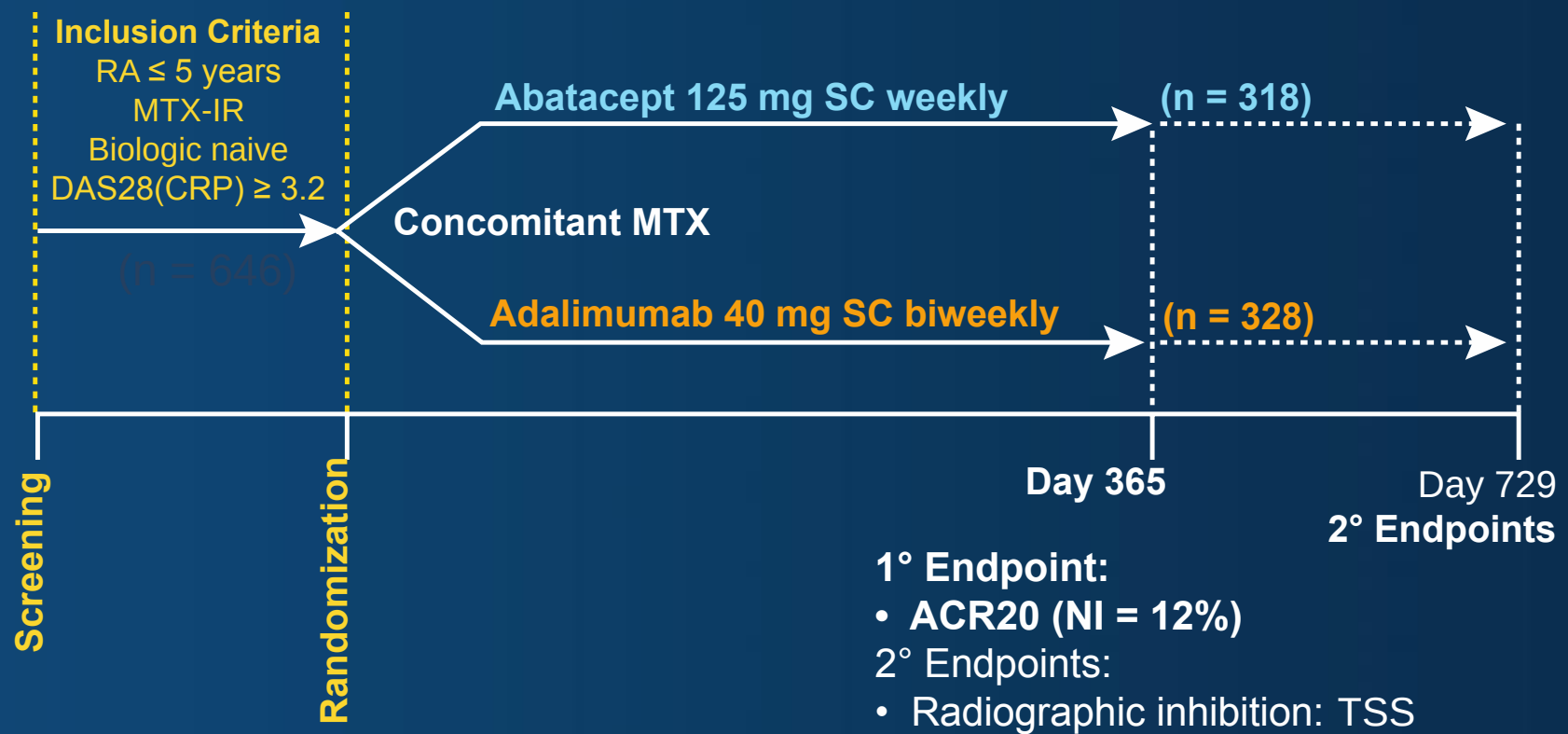
AMPLE: Abatacept vs. Adalimumab

- Prospective, multicenter, randomized, single-blind, head-to-head 2-year trial comparing abatacept & adalimumab, both administered with MTX, in RA patients
- Patients with active seropositive RA of ≤ 5 yrs duration (DAS28-CRP ≥ 3.2 + ↑ ESR or ↑ CRP) despite stable MTX 15-25 mg/wk & naïve to biologic treatment
  - Abatacept 125 mg subcut weekly
  - Adalimumab 40mg subcut every other week
- Primary endpoint: Noninferiority of SC abatacept compared to SC adalimumab, assessed by ACR20 response at 1 year

Weinblatt ME, et al. *Arthritis Rheum*. 2013; 65: 28-38.

AMPLE: Abatacept vs. Adalimumab

Noninferiority trial design (12% NI margin)



1° Endpoint:

- **ACR20 (NI = 12%)**

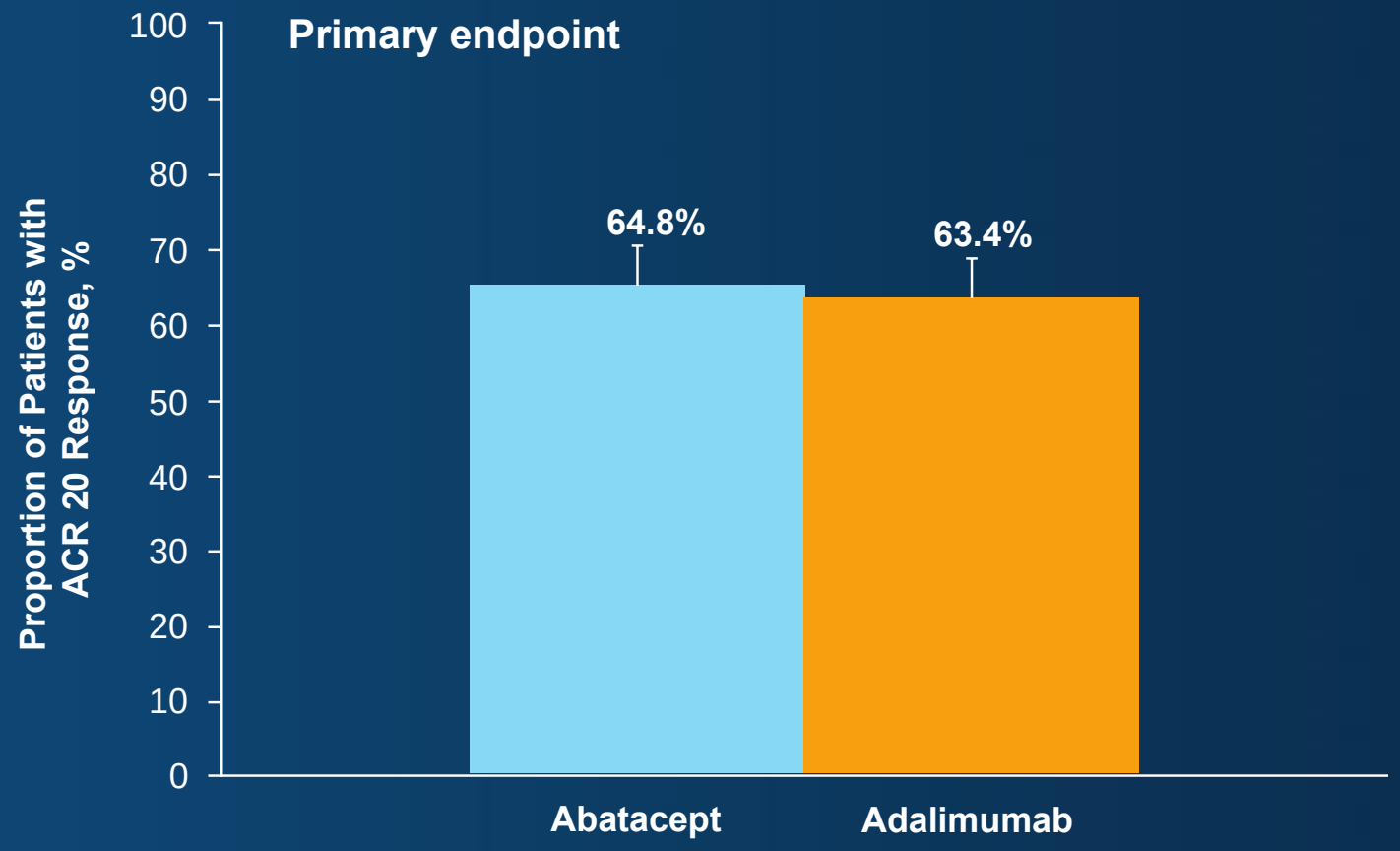
2° Endpoints:

- Radiographic inhibition: TSS
- Safety
- Injection-site reactions (prespecified)
- Retention

No IV abatacept loading dose was utilized

Weinblatt ME, et al. *Arthritis Rheum*. 2013; 65: 28-38.

AMPLE: Abatacept is Noninferior to Adalimumab ACR20 Response At 1 Year

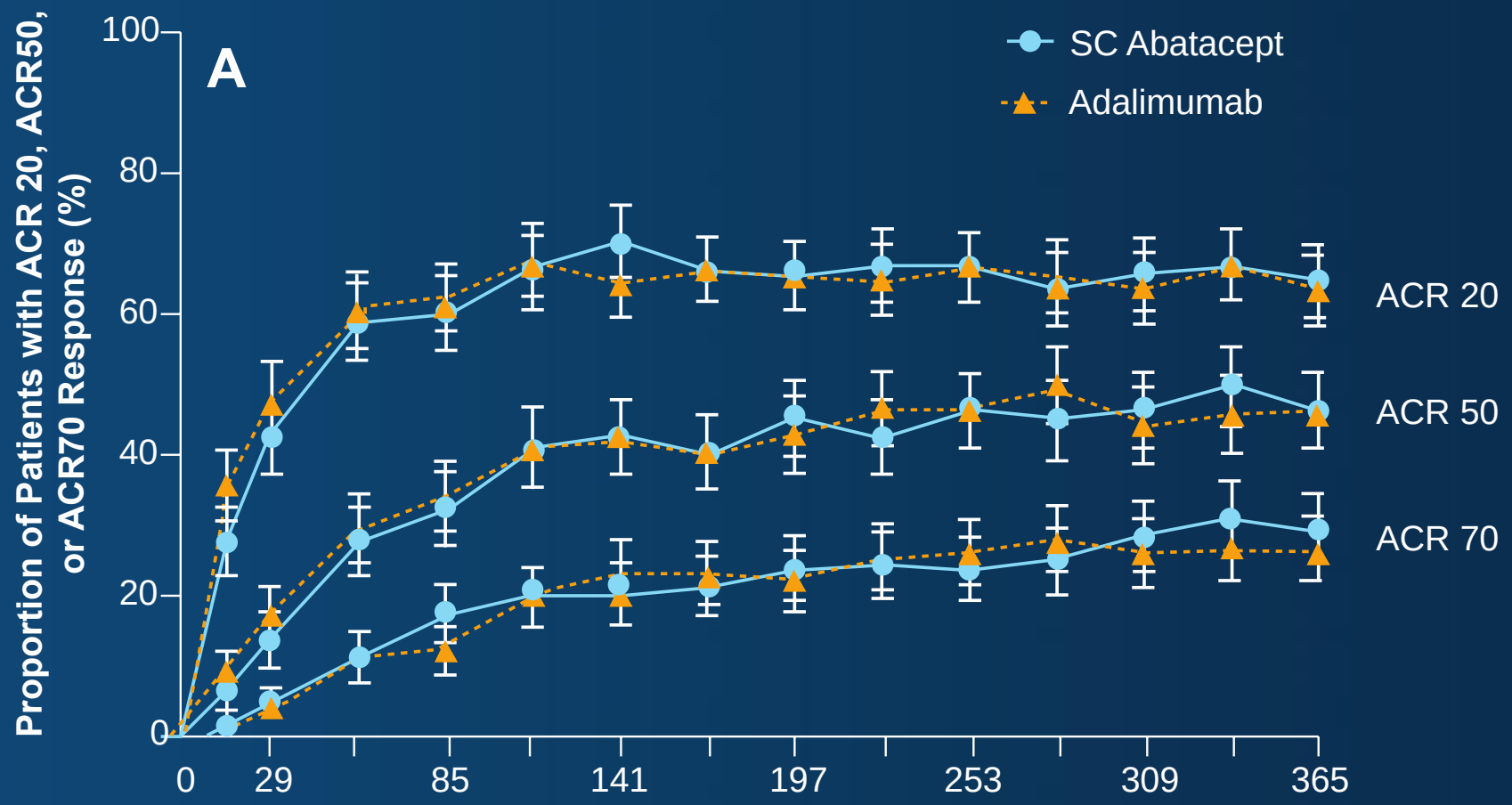


- Estimate of difference (95% CI) between groups was 1.8% (-5.6, 9.2)
  - Intent-to-treat, confirmed with per protocol population

Weinblatt ME, et al. *Arthritis Rheum*. 2013; 65: 28-38.

AMPLE: Comparable Efficacy & Kinetics of Response

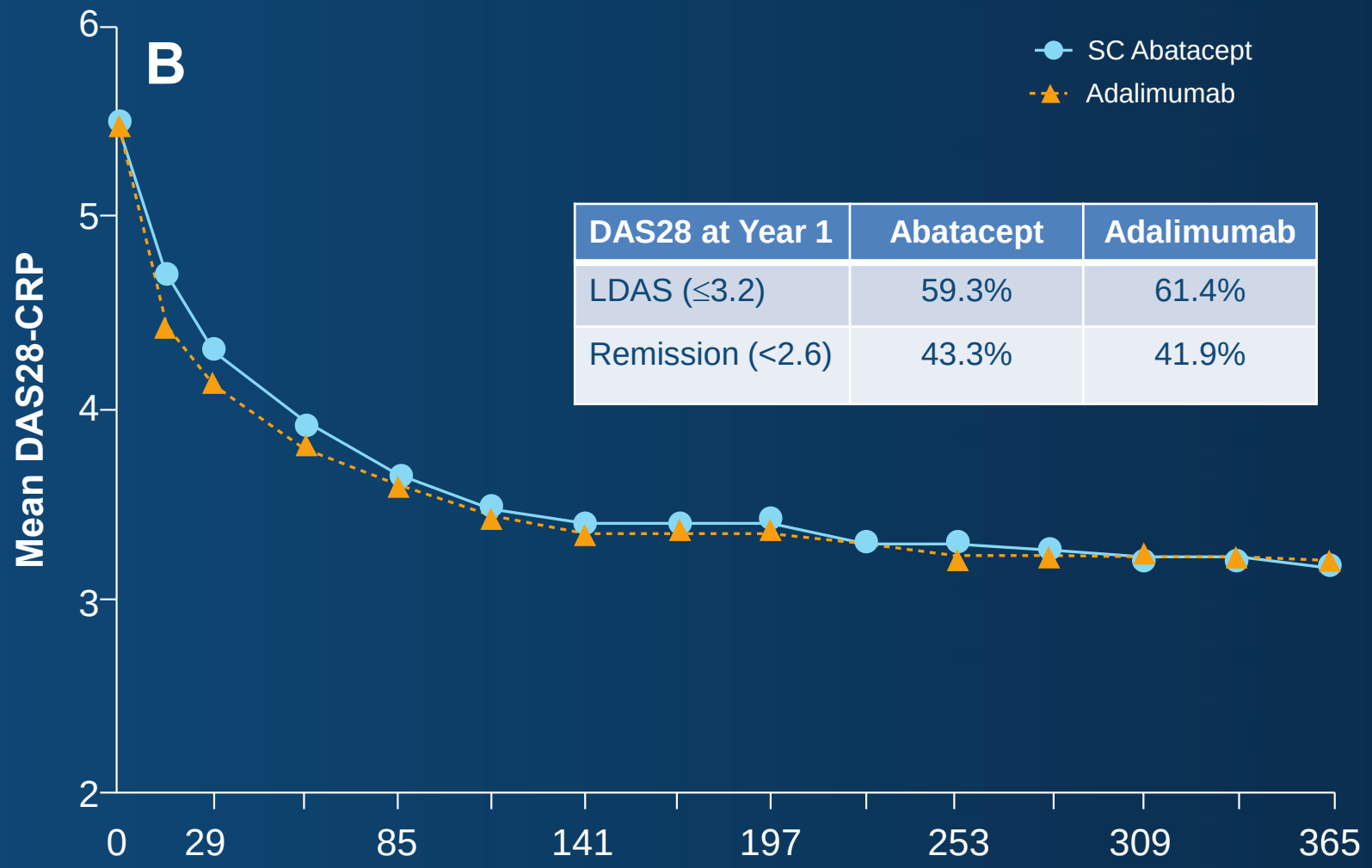
ACR Scores Over 1 Year



Weinblatt ME, et al. *Arthritis Rheum*. 2013; 65: 28-38.

AMPLE: Comparable Efficacy & Kinetics of Response

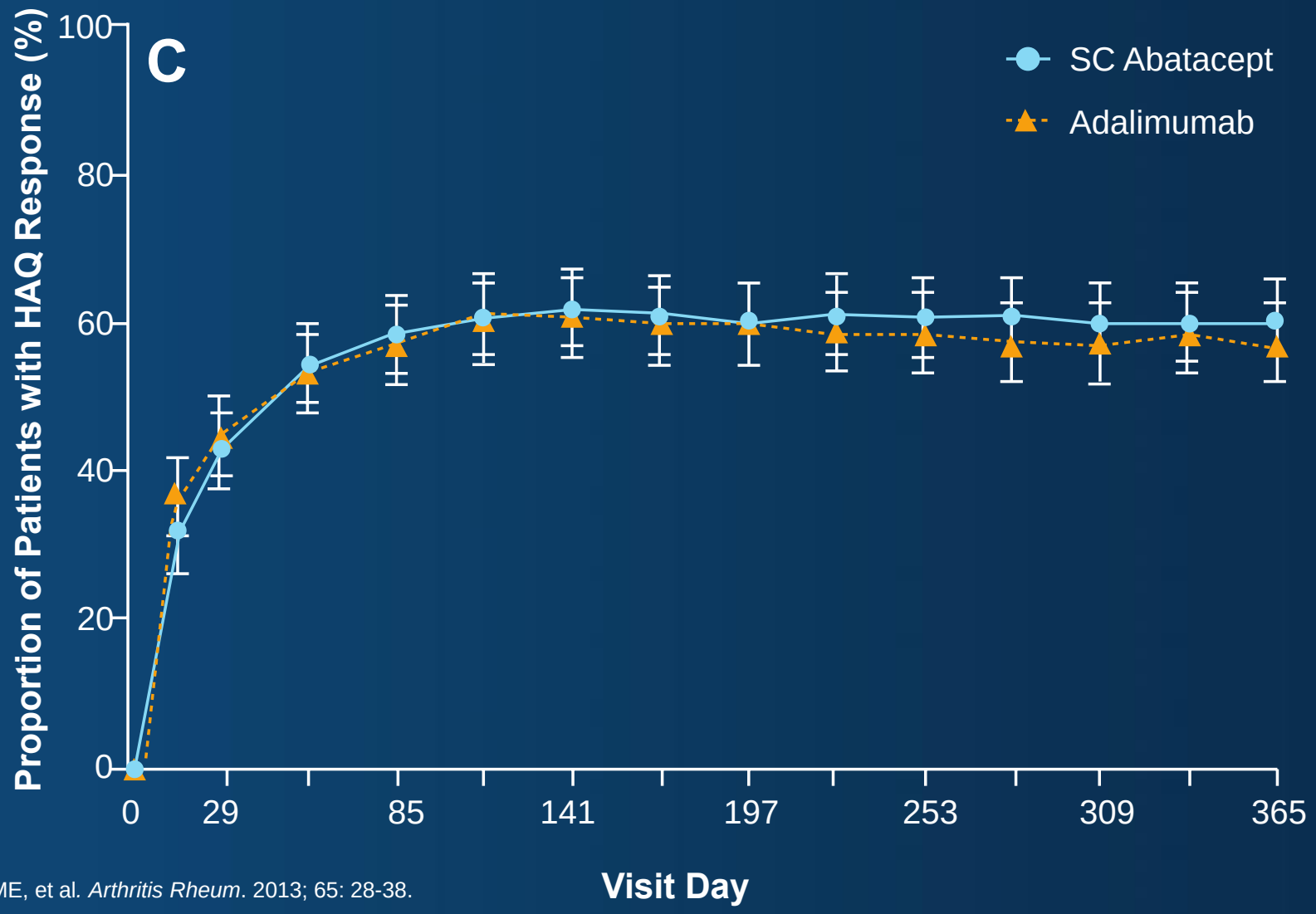
Mean DAS28 (CRP)



DAS28 at Year 1	Abatacept	Adalimumab
LDAS (≤3.2)	59.3%	61.4%
Remission (<2.6)	43.3%	41.9%

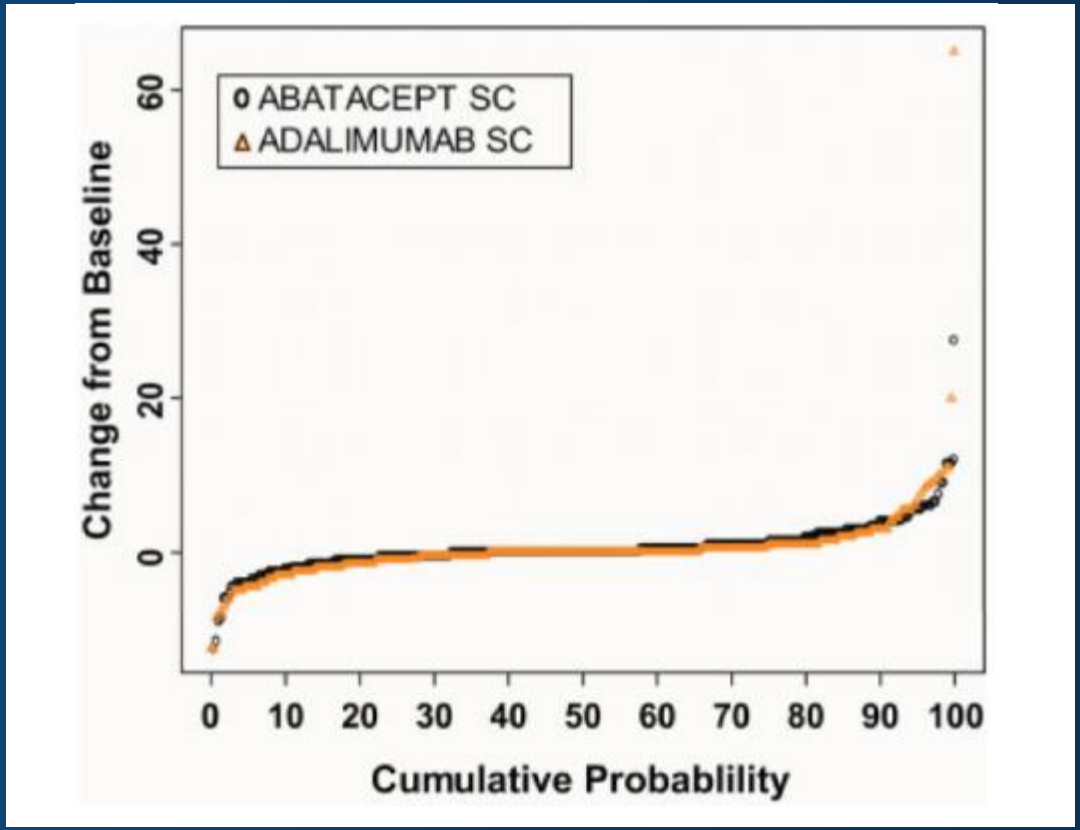
Weinblatt ME, et al. *Arthritis Rheum*. 2013; 65: 28-38.

AMPLE: Comparable Efficacy & Kinetics of Response
Physical Function Over 1 Year



Weinblatt ME, et al. *Arthritis Rheum*. 2013; 65: 28-38.

AMPLE: Similar Inhibition of Radiographic Progression Over 1 Year



- At 1 year, abatacept + MTX was similar to adalimumab + MTX in improving patient pain (53.0% & 39.2%, respectively).

Weinblatt ME, et al. *Arthritis Rheum*. 2013; 65: 28-38.

AMPLE: Safety

- Similar rates of AE, SAE, serious infections, and malignancies between both arms
- More patients with autoimmune AEs (10 vs. 4) in the abatacept arm, none of which were SAEs
- Fewer discontinuations including those due to AEs (3.5% vs. 6.1%) and those due to serious infections (none vs. 5) in the abatacept arm
- Injection-site reactions occurred in 3.8% of abatacept-treated patients vs. 9.1% of adalimumab-treated patients (P = 0.006)

Weinblatt ME, et al. *Arthritis Rheum*. 2013; 65: 28-38.

AMPLE: Abatacept vs. Adalimumab

Conclusions

- Efficacy of SC abatacept is comparable to that of SC adalimumab (by noninferiority analysis) in RA
  - Similar kinetics of response
  - Similar inhibition of radiographic progression at 1 year
- Safety was generally similar
  - Fewer discontinuations with abatacept
  - Significantly more local injection site reactions with adalimumab

Limitations

- Patients were not blinded as to treatment allocation
  - Clinical assessors were blinded to each patient's treatment
- A higher dose of adalimumab (40 mg SC weekly) is sometimes used in clinical practice, but was not included in this trial

Weinblatt ME, et al. *Arthritis Rheum*. 2013; 65: 28-38.

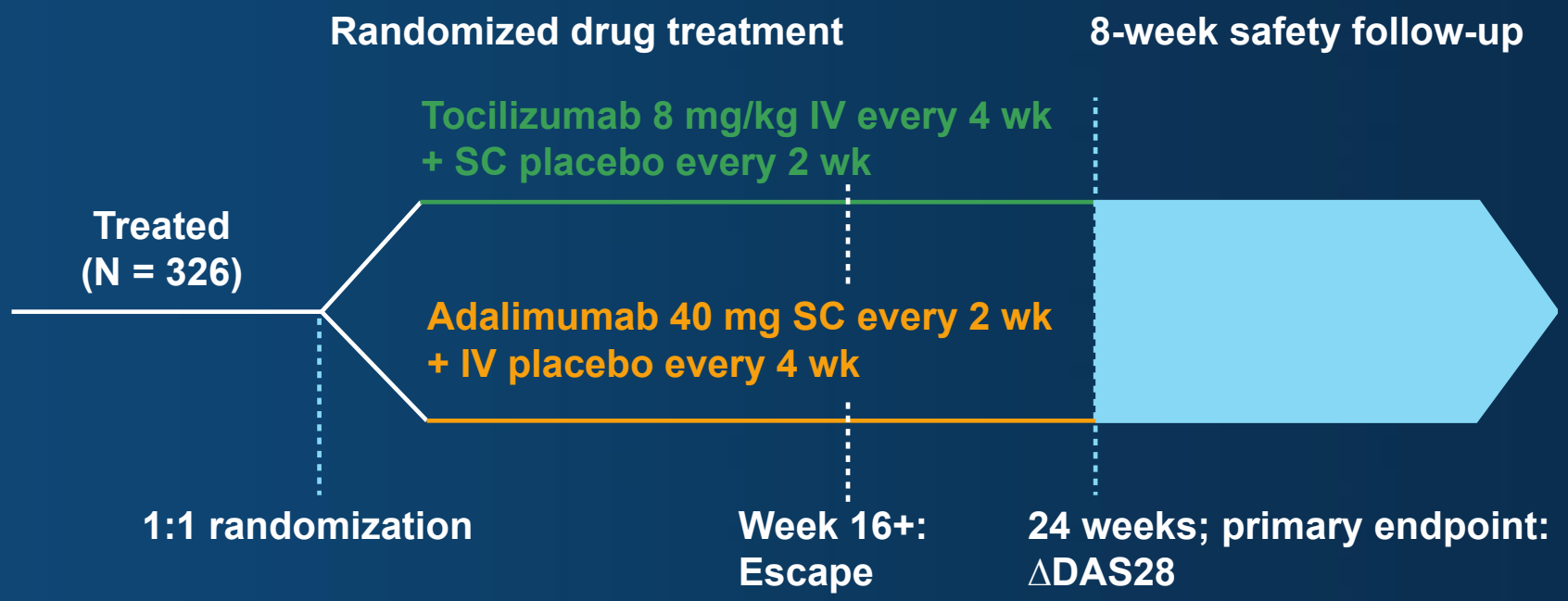
ADACTA: Tocilizumab vs. Adalimumab

- First trial specifically designed to determine superiority of one approved biologic vs. another as *monotherapy* for RA
- Phase 4 randomized, double-blind, 24-wk study in pts with RA
  - ≥6-mo duration
  - DAS28 >5.1
  - MTX intolerant *or* for whom continued treatment with MTX was considered ineffective or inappropriate

Gabay C, et al. Lancet 2013; 381: 1541–50

ADACTA: Tocilizumab vs. Adalimumab

Superiority trial design



- **Criteria for escape:** <20% improvement from baseline in SJC & TJC at week 16 or later
- **Escape therapy:** weekly SC (adalimumab/placebo) injections; study medication remained blinded

Gabay C, et al. EULAR 2012. *Ann Rheum Dis* 2012;71(Suppl3):152. Abstract LB003; Kavanaugh A, et al. 2012 ACR Annual Meeting, Abstract 772.

ADACTA: Baseline Characteristics

Basline Characteristic[a]	Adalimumab (n = 162)	Tociluzumab (n = 163)
Age, y	53.3 (12.4)	54.4 (13.0)
Female/male, %	82/18	79/21
RA duration, y	6.3 (6.9)	7.3 (8.0)
No. of previous DMARDs	2.0 (1.1)	2.0 (1.1)
Use of oral steriods, %	57	55
Disease activity		
DAS28	6.8 (0.9)	6.7 (0.9)
TJC (28 joints)	16.5 (7.0)	15.9 (6.7)
SJC (28 joints)	12.4 (5.4)	11.3 (5.3)
CDAI	43.1 (12.6)	41.0 (12.3)
ESR, mm/h	45.5 (25.4)	50.5 (29.0)
CRP, mg/dL	2.5 (3.9)	2.6 (3.1)
Patient VAS, mm	73.4 (19.4)	71.2 (20.8)
HAQ	1.7 (0.6)	1.6 (0.6)

Data are presented as mean (SD), unless otherwise indicated

Gabay C, et al. EULAR 2012. *Ann Rheum Dis* 2012;71(Suppl3):152. Abstract LB003; Kavanaugh A, et al. 2012 ACR Annual Meeting, Abstract 772.

ADACTA: Change in DAS28 From Baseline to Week 24 (ITT Population*)

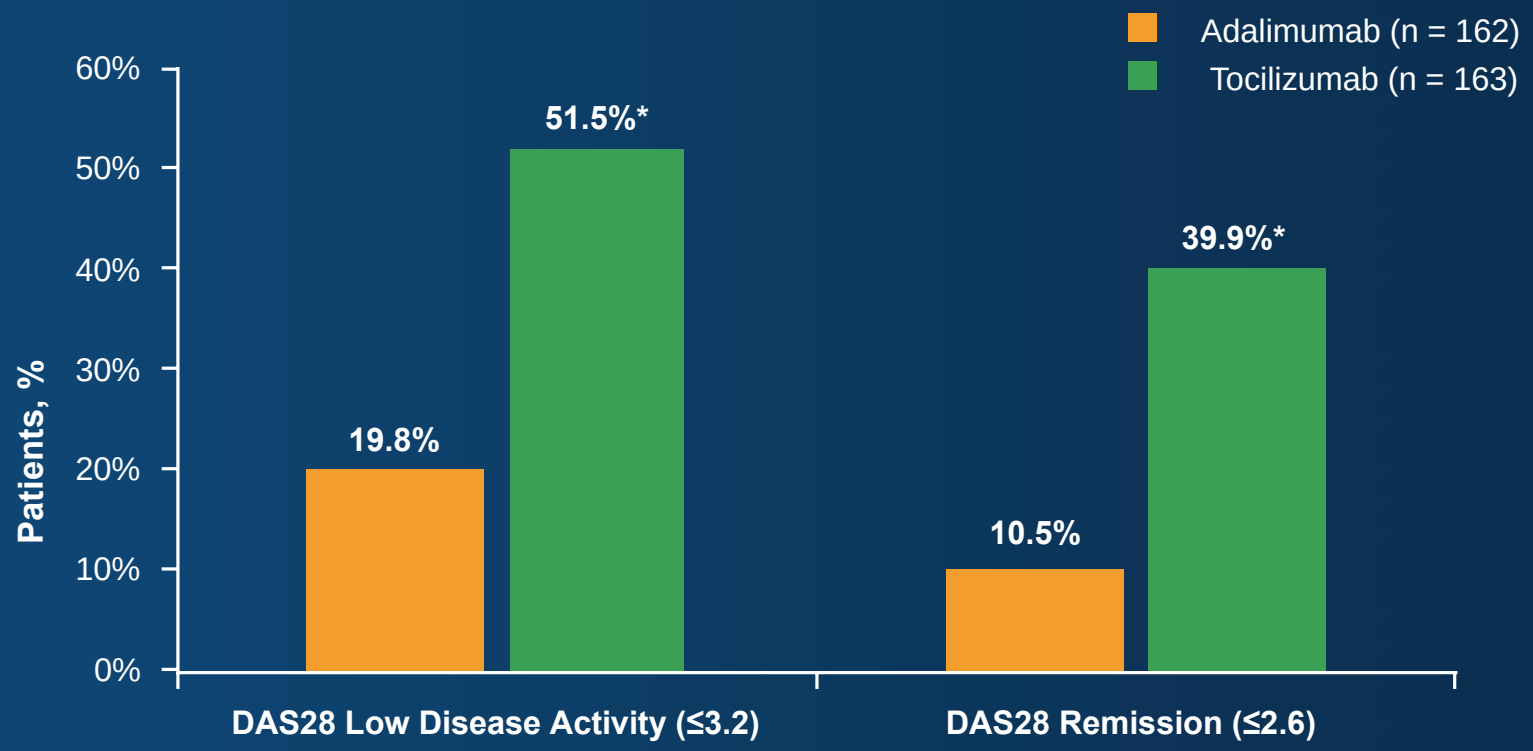
Δ in Baseline to Week 24†	Adalimumab 40 mg SC + IV Placebo (n = 162)	Tociluzumab 8 mg/kg IV + SC Placebo (n = 163)
Adjusted mean	-1.8	-3.3
Difference	-1.5	
95% CI for difference	-1.8 to -1.1	
P value	< 0.0001	

*LOCF & non-responder imputation analysis.

†Analysis of variance (model included baseline value plus the stratification factors of region and duration of RA. 1 adalimumab patient did not receive treatment; 2 tocilizumab patients had no post-baseline data & were excluded from the analysis.

Gabay C, et al. EULAR 2012. *Ann Rheum Dis* 2012;71(Suppl3):152. Abstract LB003; Kavanaugh A, et al. 2012 ACR Annual Meeting, Abstract 772.

ADACTA: Patients With DAS28 Remission/LDA at Week 24 (ITT Population†)

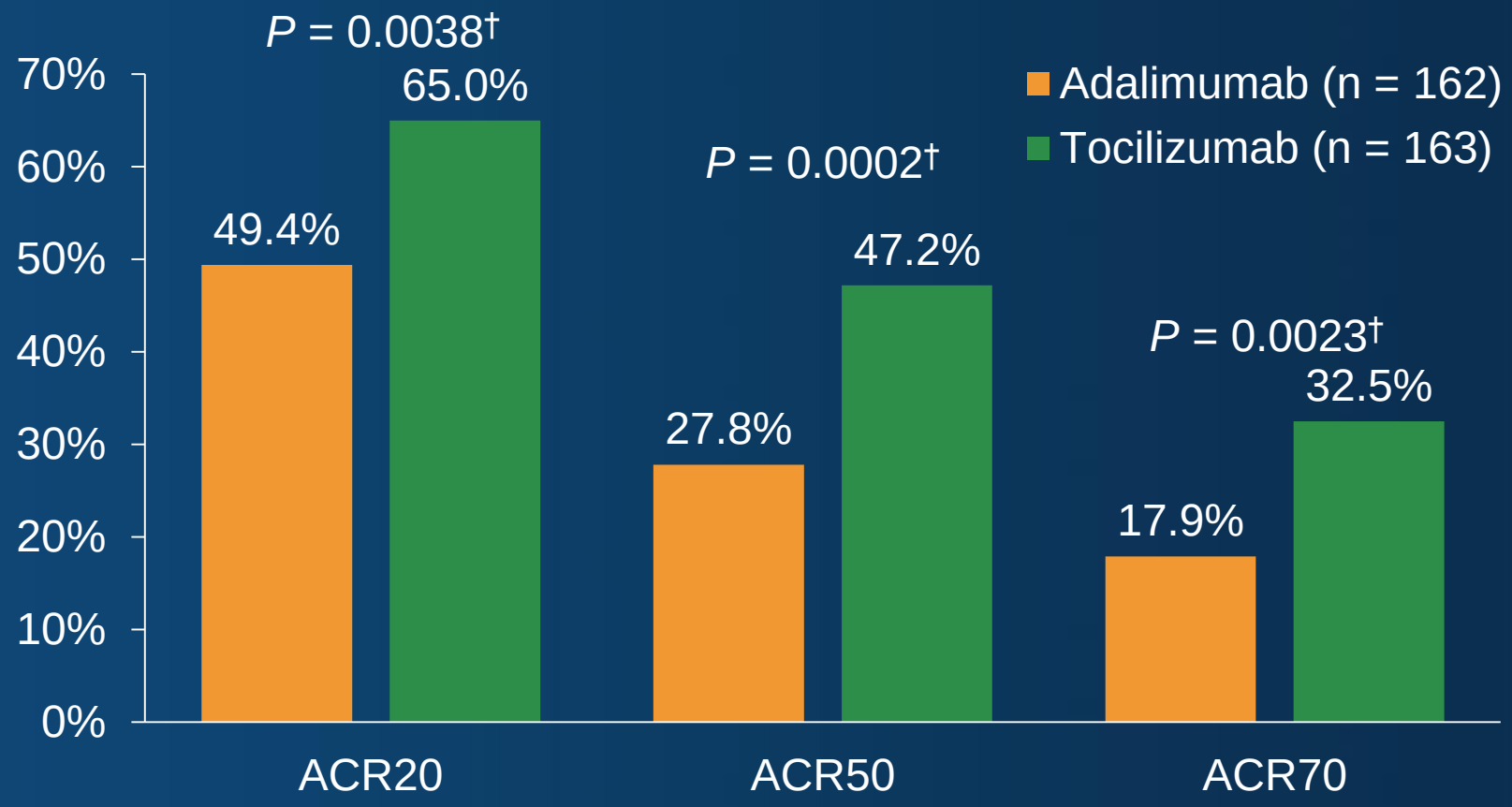


†LOCF & non-responder imputation analysis.

*$P < 0.0001$ (vs. adalimumab); significance was determined using a logistic regression analysis (covariates included treatment, region, and duration of RA).

Gabay C, et al. EULAR 2012. *Ann Rheum Dis* 2012;71(Suppl3):152. Abstract LB003; Kavanaugh A, et al. 2012 ACR Annual Meeting, Abstract 772.

ADACTA: ACR Responses at Week 24 (ITT Population*)



*LOCF & non-responder imputation analysis.

†*P* values were determined using a logistic regression analysis (covariates included treatment, region, and duration of RA).

Kavanaugh A, et al. 2012 ACR Annual Meeting, Abstract 772.

ADACTA: Exploratory & Post Hoc Endpoints at Week 24 (ITT Population*)

	Adalimumab 40 mg SC + IV Placebo (n = 162)	Tociluzumab 8 mg/kg IV + SC Placebo (n = 163)	P value†
CDAI remission	9.3%	17.2%	0.0389
SDAI remission	8.0%	18.4%	0.0067
ACR/EULAR remission (Boolean)	11.0%	18.0%	0.0569
Δ from baseline in HAQ-DI	-0.5	-0.7 (diff: -0.2)	0.0653

*LOCF & non-responder imputation analysis.

†P value was not adjusted for multiple testing & controlling of type 1 error; therefore, no statistical significance claims can be made.

Kavanaugh A, et al. 2012 ACR Annual Meeting, Abstract 772.

ADACTA: Safety

- Similar incidence between groups of:
  - AEs: tocilizumab: 82.1%; adalimumab: 82.7%
  - SAEs: tocilizumab: 11.7%; adalimumab: 9.9%
  - Serious infections: tocilizumab: 3.1%; adalimumab: 3.1%
- Laboratory abnormalities occurred in both arms, but were more common with TCZ
  - ↑ hepatic transaminases
  - ↑ LDL
  - ↓ neutrophil counts
- Two deaths occurred, both in the tocilizumab arm:
  - Sudden death
  - Reported illicit drug overdose

Gabay C, et al. EULAR 2012. *Ann Rheum Dis* 2012;71(Suppl3):152. Abstract LB003; Kavanaugh A, et al. 2012 ACR Annual Meeting, Abstract 772.

Implications of Data from Head-to-Head Trials

- What is the significance of the different RA populations in these studies?
  - MTX-IR, continuing MTX
  - TNF-IR
  - Patients not willing or able to take MTX, receiving biologic monotherapy
- Implications of study design
  - Non-inferiority vs. superiority
  - Magnitude of differences: clinically meaningful or not?
- How can/should CER data guide daily clinical practice?
- What are the most compelling CER questions yet unanswered?

Comparative Effectiveness Studies of Biologics in RA: Summary

- Switching MOA be more effective than TNF cycling for patients who are TNF-IR
- Abatacept & infliximab demonstrated similar efficacy, abatacept with better safety
- Head-to-head study of SC abatacept + MTX vs. SC adalimumab + MTX in MTX-IR patients: comparable efficacy and safety
- Head-to-head study of tocilizumab monotherapy vs. adalimumab monotherapy favored tocilizumab

Finckh A, et al. *Arthritis Rheum*. 2007; 56: 1417-1423; Rubbert-Roth A, et al. 2012 ACR Annual Meeting, Abstract 467.
Schiff M et al. *Ann Rheum Dis* 2008; 67: 1096-1103. Harold LR et al. *Ann Rheum Dis*. 2015 Feb;74(2):430-6