TREATMENT ADJUSTMENT AFTER FAILURE OF FIRST ANTI-TNF:
MAXIMISING BENEFITS FOR PATIENTS

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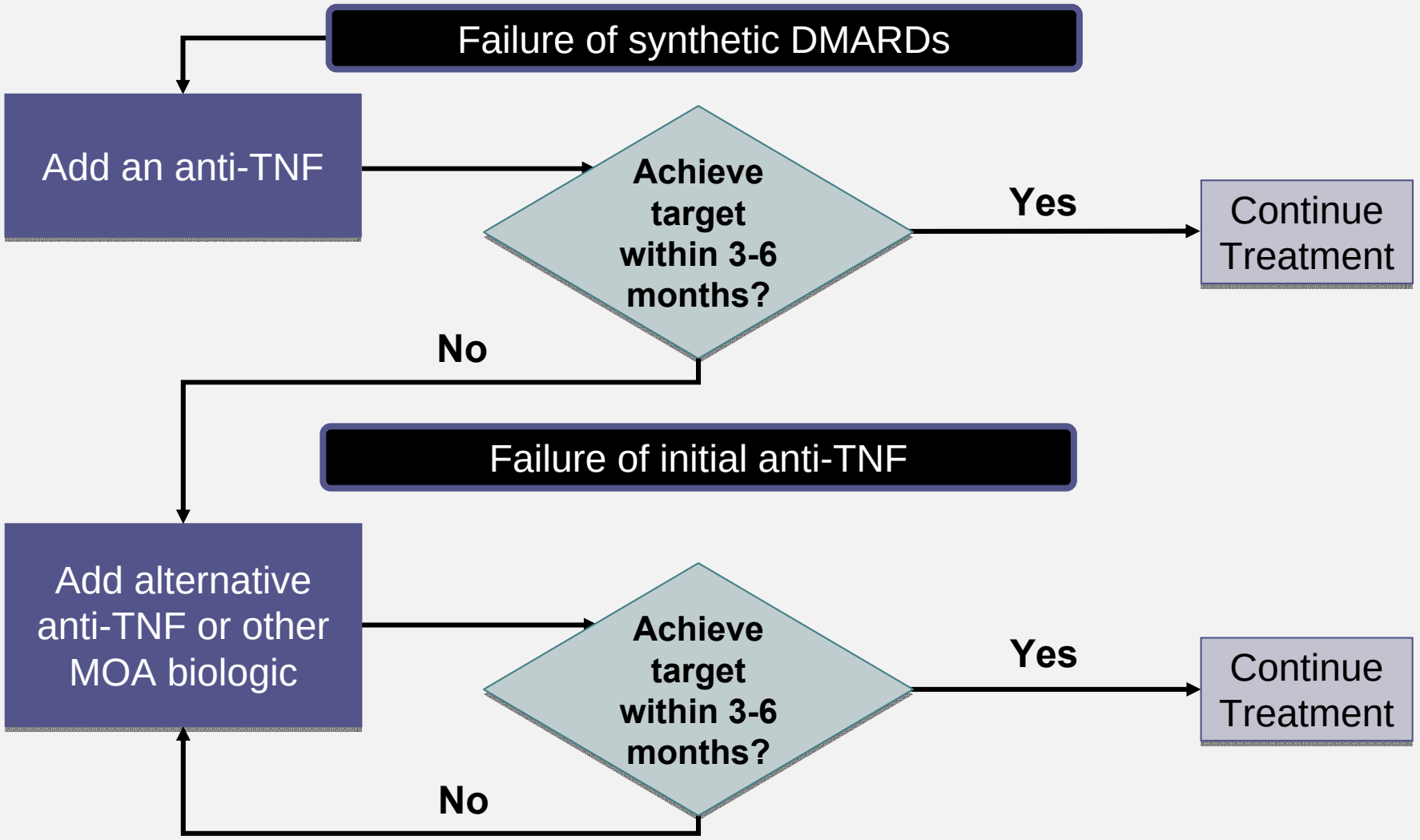
Overview

- EULAR Recommendations
- Clinical Data
  - Switching between anti-TNFs
  - Switching to other biologics
- Maximising Benefit for the Patient
  - Why should you switch?
  - When should you switch?

RA Treatment Algorithm



Smolen et. al. Ann Rheum Dis. 2010 Jun;69(6):964-75

EULAR Recommendations

8. In patients responding insufficiently to MTX and/or other synthetic DMARDs with or without GCs, biological DMARDs should be started; current practice would be to start a TNF inhibitor (adalimumab, certolizumab, etanercept, golimumab, infliximab) which should be combined with MTX

9. Patients with RA for whom a first TNF inhibitor has failed, should receive another TNF inhibitor, abatacept, rituximab or tocilizumab.

Smolen et. al. Ann Rheum Dis. 2010 Jun;69(6):964-75

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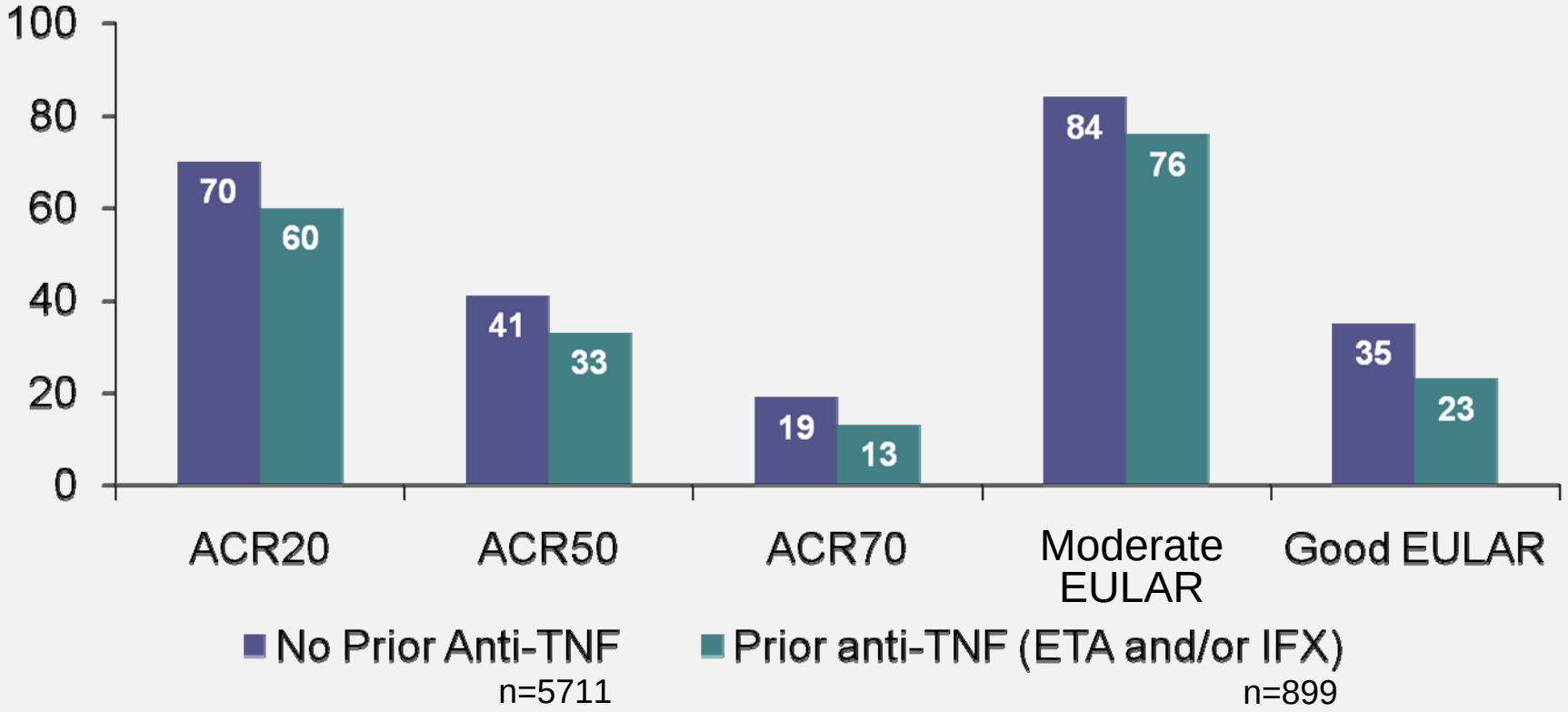
Treatment Adjustment - ReACT: Switch to Adalimumab

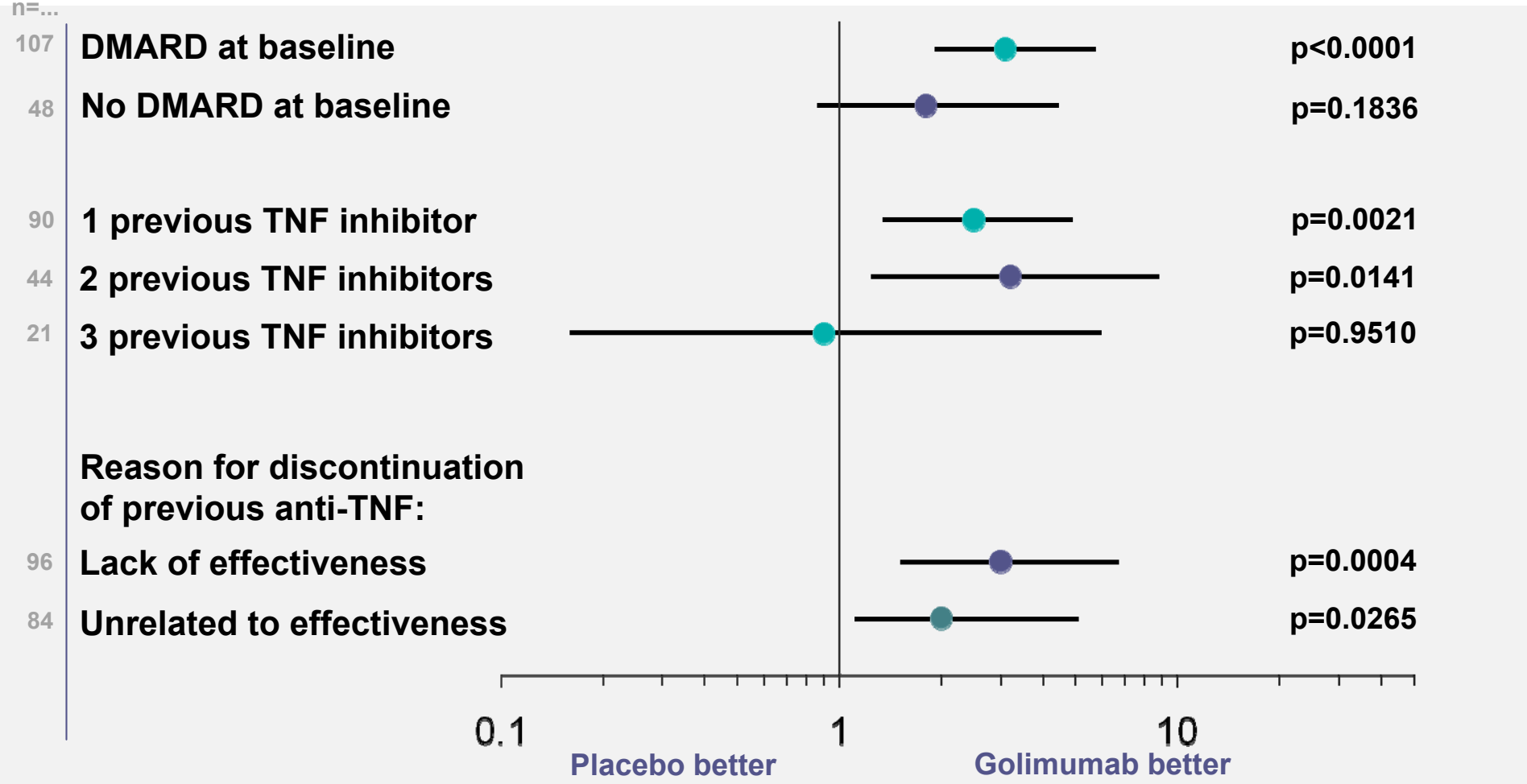
ReAct – Research in Active Rheumatoid Arthritis

Analysis of 12 week outcomes in patients who switched to adalimumab and had previously been treated with etanercept or infliximab



Bombardieri et. al. Rheumatology 2007;46:1191–1199

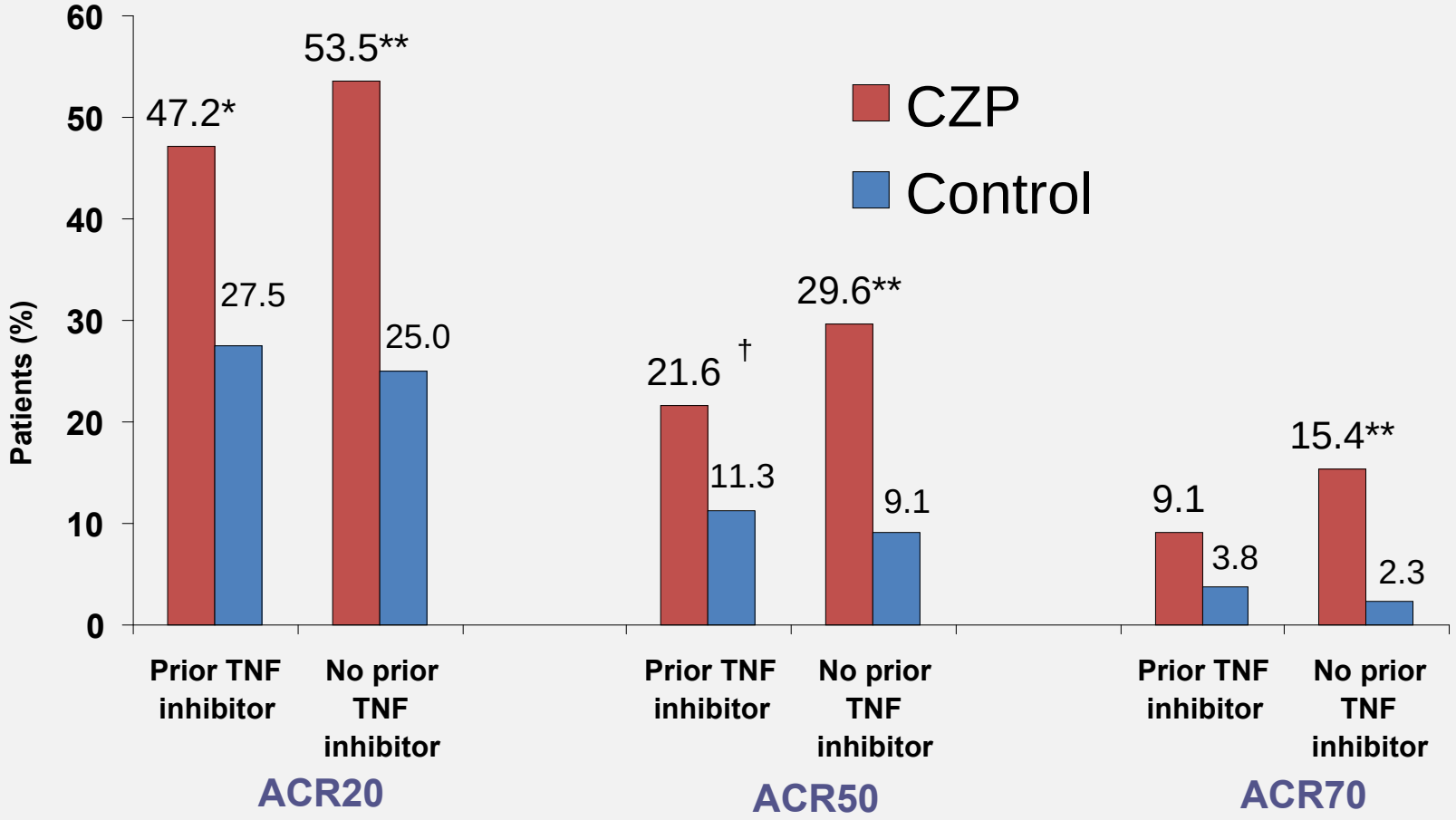
Treatment Adjustment - GO-AFTER: Switch to Golimumab



* combined golimumab 50 mg and 100 mg groups
Golimumab 100 mg is not an approved dosing regimen

Smolen et. al. Lancet 2009; 374: 210–21

Treatment Adjustment - REALISTIC: Switch to Certolizumab Pegol



*p<0.01; **p<0.001; †p<0.05 vs control.

Prior TNF inhibitor: CZP (n=320), control (n=80); no prior TNF inhibitor: CZP (n=531), control (n=132).

CZP dose: 400 mg at Weeks 0, 2, and 4. 200 mg at Weeks 6, 8, and 12.

Weinblatt et al. Abstract 1805, ACR 2010

Switching Between anti-TNFs

Groups	HAQ at start of first anti-TNF therapy	Mean change in HAQ on first anti-TNF therapy (between start and first designation of failure)	Adjusted change in HAQ over 12 months (95% CI)	Patients with >0.22U improvement in HAQ (%) over subsequent 12 months	p value
Stoppers (n=148)	2.21	-0.03	Referant	22	-
Stayers (n=389)	2.08	-0.13	-0.12 (-0.23, -0.02)	31	0.01*
All Switchers (n=331)	2.15	-0.05	-0.15 (-0.26, -0.05)	36	0.19**
Early Switchers (n=147)	2.10	-0.07	-0.18 (-0.31, -0.06)	42	0.03**

- Many patients who fail to respond to one anti-TNF agent switch to a second anti-TNF drug.
- A significant proportion of these patients will demonstrate improvements in HAQ score on their second drug.

* vs. stoppers ** vs. stayers

Hyrich et. al. Rheumatology 2008;47:1000–1005

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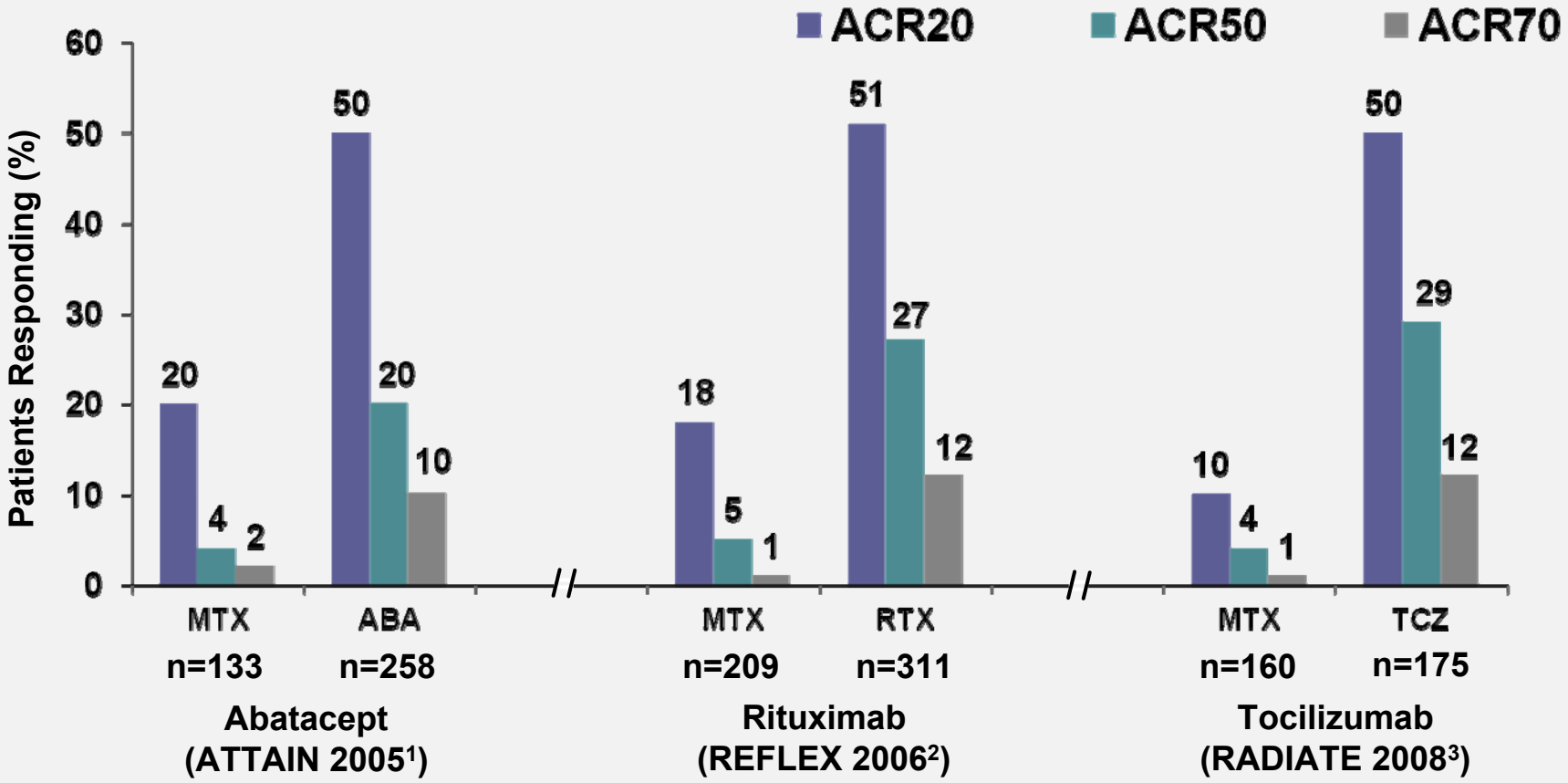
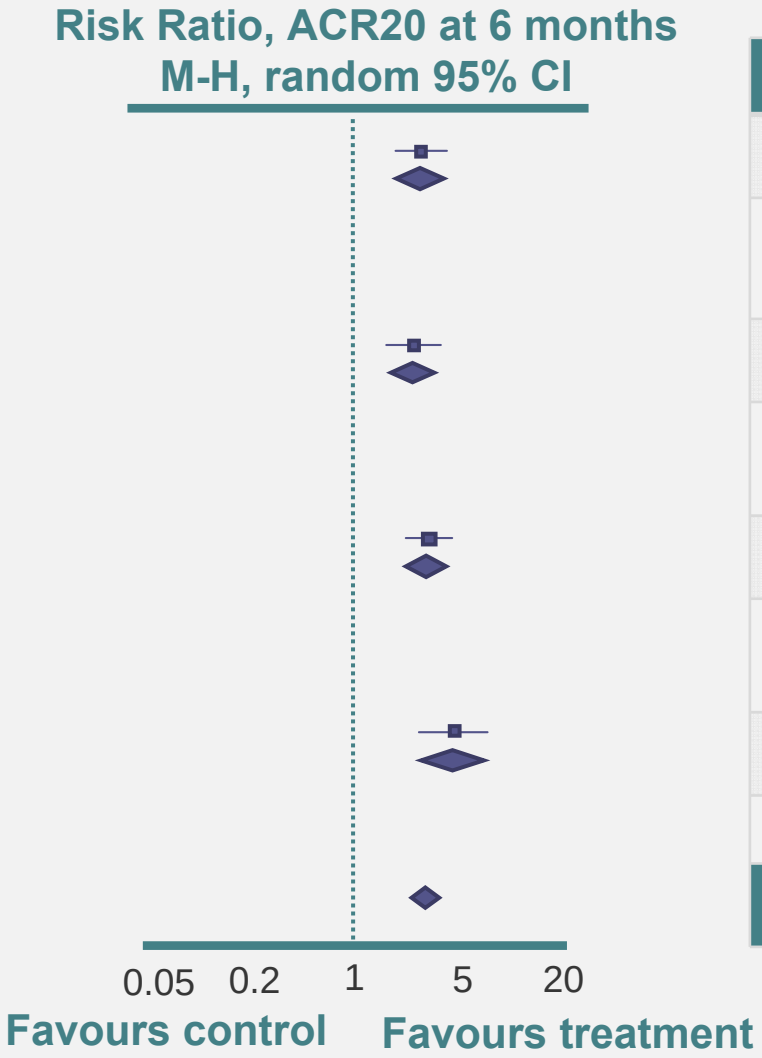
Other Biologics in anti-TNF Non-responders

Randomised, placebo-controlled, phase III trials for biologics in patients with inadequate response to anti-TNFs – ACR response at 6 months



1. Genovese et al. N Engl J Med 2005;353:1114-23
2. Cohen SB et al. Arthritis Rheum. 2006 Sep;54(9):2793-806
3. Emery P et al. Ann Rheum Dis 2008;67;1516-1523

Other Biologics in anti-TNF Non-Responders



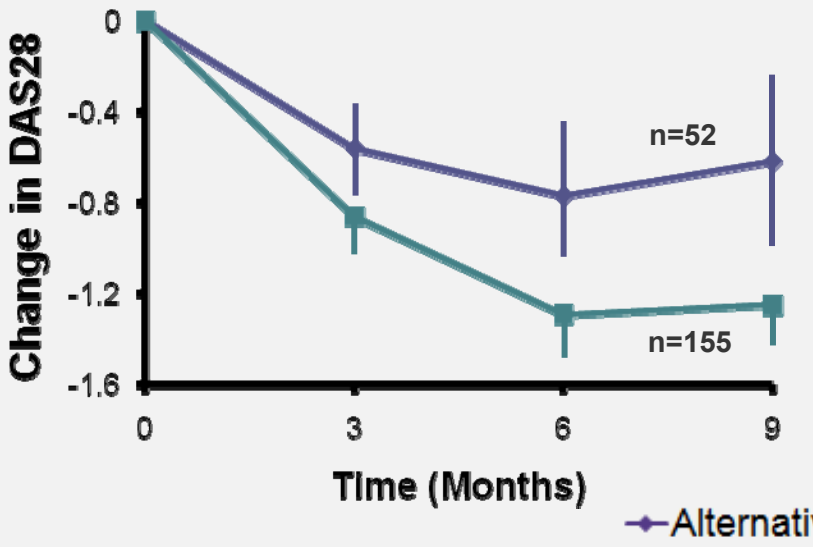
Biological DMARD	Risk Ratio (95%CI)
Abatacept	2.56 (1.77-3.69)
Golimumab	2.32 (1.59-3.38)
Rituximab	2.85 (2.08-3.91)
Tocilizumab	4.00 (2.47-6.48)
Total	2.78 (2.28-3.38)

Nam et. al. Ann Rheum Dis. 2010 Jun;69(6):976-86

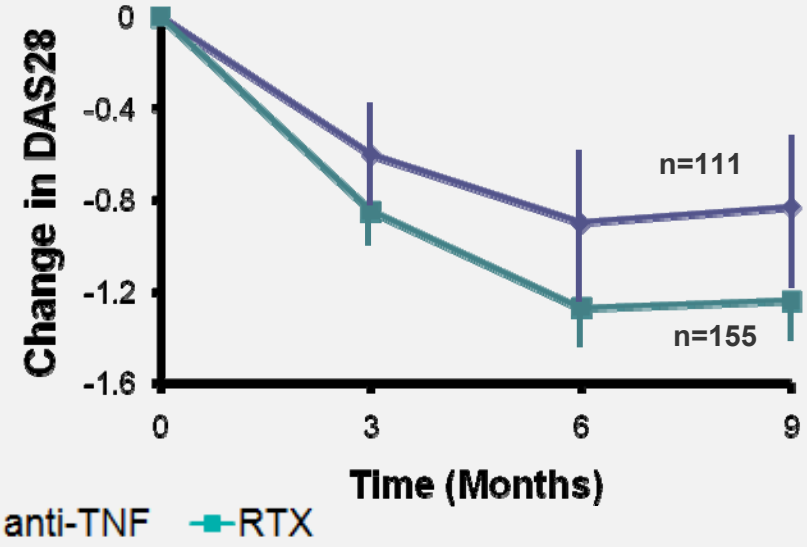
Switching to Rituximab

Study of cohort of RA patients from the Swiss RA registry who discontinued at least one anti-TNF and switched to another

Switch from anti-TNF: mAB to mAB or RTX



Switch from anti-TNF: SR to mAB or RTX



Alternative anti-TNF — RTX

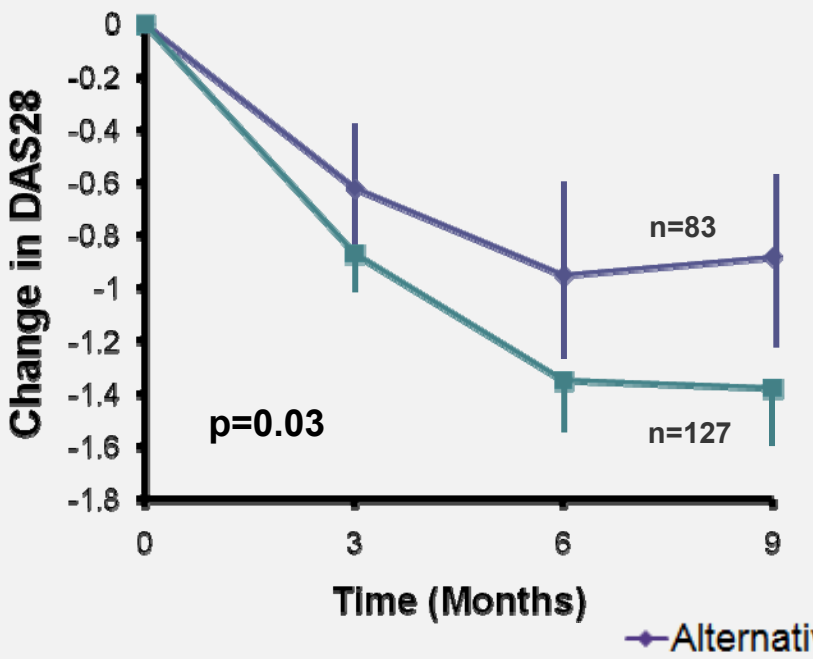
Improvements in DAS28 are more favourable with RTX than alternative anti-TNF

mAB = Antibody SR = Soluble Receptor

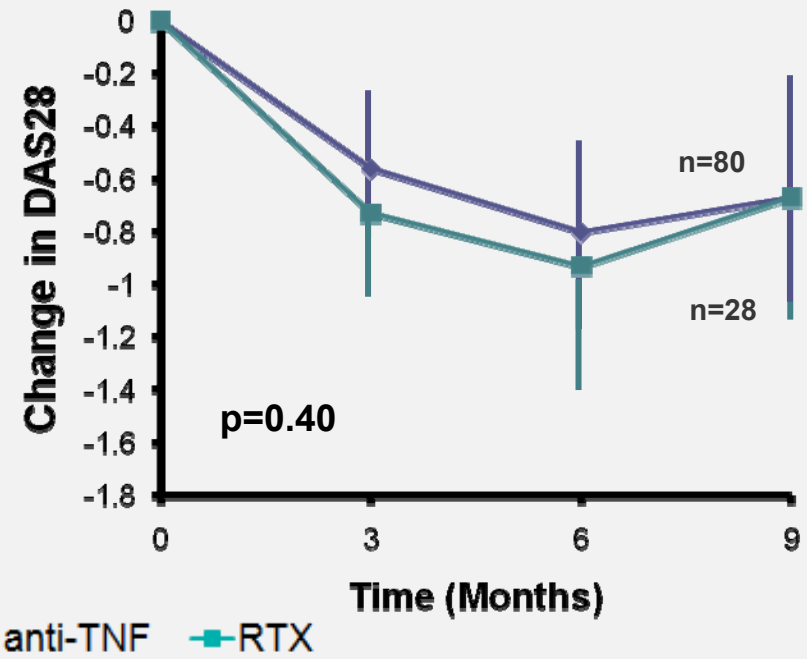
Finckh et. al. Ann Rheum Dis 2010;69:387–393

Switching to Rituximab

Switch due to therapeutic anti-TNF resistance



Switch due to adverse effects



Alternative anti-TNF — RTX

Switching to a biologic with a different mechanism of action is more effective than switching to another anti-TNF after loss of efficacy of the initial anti-TNF

Finckh et. al. Ann Rheum Dis 2010;69:387–393

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Why Should You Switch?

- **Lack of efficacy**
  - Primary non-response
  - Secondary loss of response
- **Toxicity**
  - High incidence of adverse effects

Switching Between anti-TNFs

Study of cohort of RA patients from BSRBR, the UK national register of new anti-TNF treatment starts.

Risk analysis of those patients who switched treatment during the 15 month follow-up period.

Reason for initial switch	Adjusted hazard ratios for stopping second anti-TNF (95% CI)	
	Due to inefficacy	Due to adverse event
Inefficacy (n=503)	**2.7 (2.1-3.4)**	1.1 (0.9-1.5)
Adverse Event (n=353)	1.2 (0.8-1.6)	**2.3 (1.9-2.9)**

- The reason for switching from the first anti-TNF may be predictive for the outcome of the second.

Hyrich et.al. Arthritis Rheum. 2007 Jan;56(1):13-20

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Early switchers showed a greater improvement at 12 months than those who switched later.

*** vs. stoppers** **** vs. stayers**

Hyrich et. al. Rheumatology 2008;47:1000–1005

Predicting Treatment Response

Observational cohort study in Southern Sweden of patients receiving the anti-TNFs ETA, IFX or ADA.

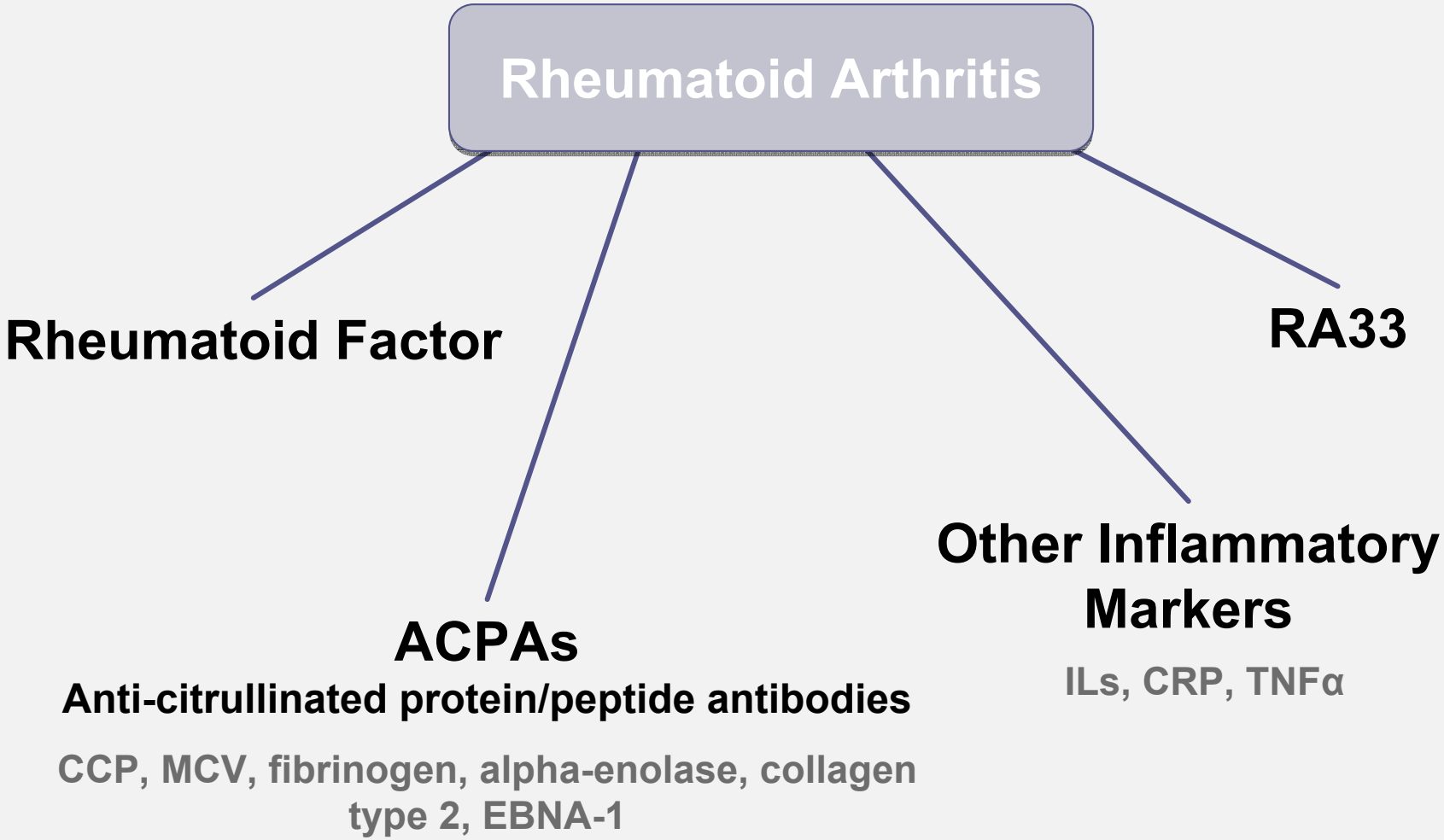
Investigation into whether response at 6 weeks and 3 months predicts continuation of treatment

Response/ Disease State	Hazard ratio for stopping TNF-inhibitor (95%CI)			
	6 weeks	P value	3 months	P value
ACR20	0.55 (0.43-0.71)	**<0.001**	0.56 (0.47-0.66)	<0.001
ACR50	0.64 (0.48-0.85)	**0.002**	0.55 (0.46-0.66)	<0.001
ACR70	1.06 (0.59-1.90)	0.850	0.56 (0.42-0.75)	<0.001
EULAR remission	1.03 (0.65-1.62)	0.911	**0.65 (0.51-0.82)**	**<0.001**
SDAI remission	1.85 (0.86-4.02)	0.118	**0.60 (0.41-0.87)**	**0.006**
CDAI remission	1.82 (0.84-3.95)	0.129	**0.64 (0.44-0.92)**	**0.016**

- ACR20 and ACR50 responses as early as 6 weeks after treatment initiation are significant predictors of continuation of TNF-inhibitor therapy

Gulfe A et al. J Rheumatol. 2009;36:517-521

Biomarkers in RA



Biomarkers in RA

Plasma profile analysis of anti-TNF naive RA patients with either response or non-response to 30 weeks of infliximab treatment

Biomarkers apolipoprotein A-I and platelet factor 4 were characterised

- Platelet factor 4 significantly higher in NR
- Apolipoprotein-AI significantly higher in R

Studies in a larger cohort of patients must be carried out to validate these findings

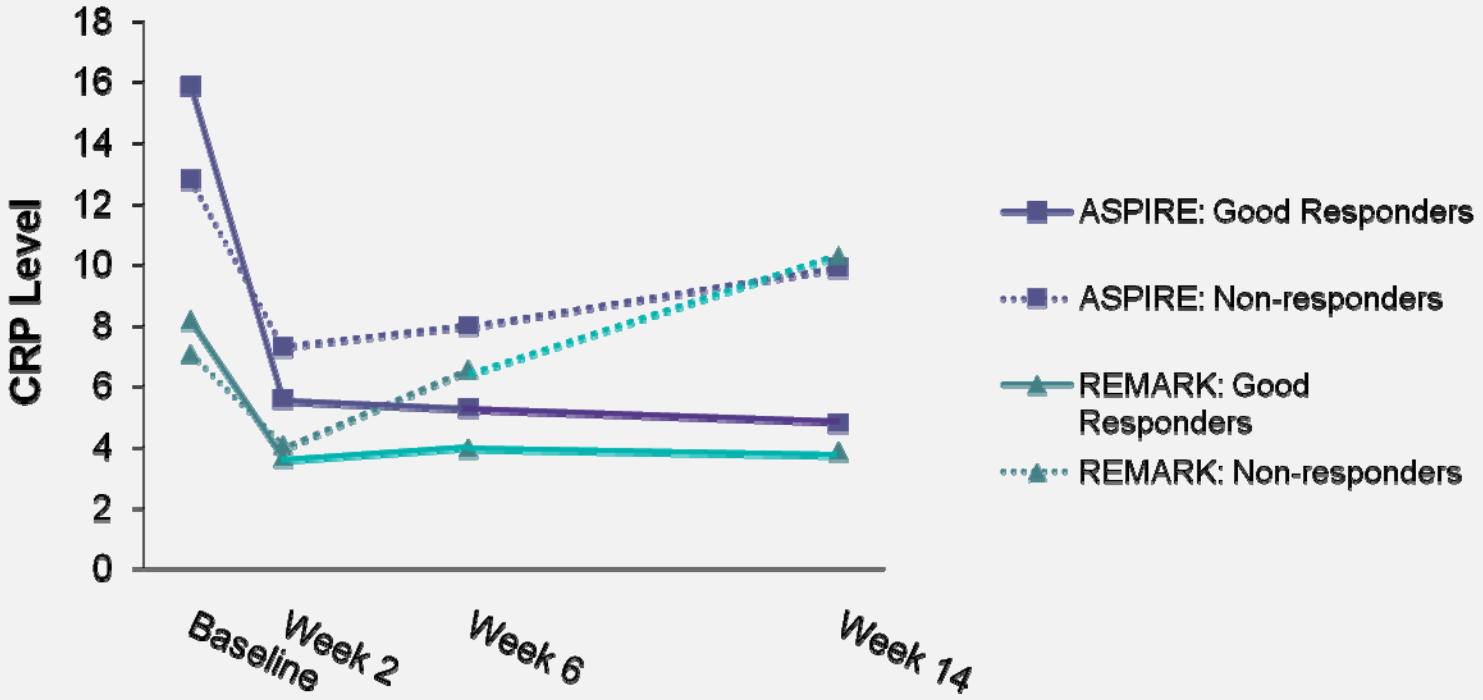
AP-AI and PF4 may be key elements in RA treatment monitoring

Trocmé et al. Ann Rheum Dis. 2009 Aug;68(8):1328-33.

Biomarkers in RA: CRP

Analysis of clinical data from REMARK and ASPIRE trials

Changes in C-reactive Protein levels associated with clinical response to infliximab



Adapted from Meeuwisse et al. AB0303, EULAR 2010

Biomarkers in RA: Rheumatoid Factor

Assessment of clinical factors associated with a major response to rituximab in patients with an inadequate response to prior anti-TNFs

	Odds Ratio	95% CI	p value
Variables associated with ACR50 response			
Lower HAQ	0.233	0.09-0.605	0.03
Lower number of previous anti-TNFs	0.465	0.239-0.905	0.024
RF positivity	24.566	3.926-153.7	0.001
Variables associated with EULAR moderate to good response			
RF positivity	7.5	2.216-25.380	0.001

Quartuccio et al. Rheumatology 2009;48:1557–1559

Biomarkers in RA: Seropositivity

- Post-hoc analysis looked at a pooled cohort from 2 Phase III studies
- At week 24, seropositive patients were more than twice as likely to achieve an ACR response (ACR20 or ACR50) than those who were seronegative.
- At week 48 seropositive patients were over three times more likely to achieve a 70% improvement in symptoms (ACR70) compared to seronegative patients (20.9% vs. 6.9%).
- Seropositive patients also had significantly greater reduction in DAS28, and were more likely to achieve a low disease status by week 48.

Seropositive patients respond more favourably to RTX treatment

Isaacs et al. FRI 0256 EULAR 2009, http://www.roche.com/media/media_releases/med-cor-2010-06-17.htm

Summary

- New EULAR guidelines recommend treatment adjustment every 3 months until treatment targets are reached
- After failure of an initial anti-TNF the recommendation is to switch to a different anti-TNF or another biologic
- Data from clinical trials suggests switching between anti-TNFs and to other biologics can be successful depending on the reason for initial switch
- There is limited data available on predicting treatment response to biologics
- More investigation is needed in finding biomarkers to help predict treatment response when switching therapies