’ Therapeutic target in Axial SpA: does remission make the difference?'

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Defining remission in axSpA

Sieper. Defining remission in ankylosing spondylitis. Ann Rheum Dis 2012. 71(Supp2):i93-95

- Clinical remission
- Absence of objective inflammation eg CRP/ MRI
- Prevention of structural damage
- Reaching normal function
- Remission of EAMs

Remission in axSpA

Clinical remission

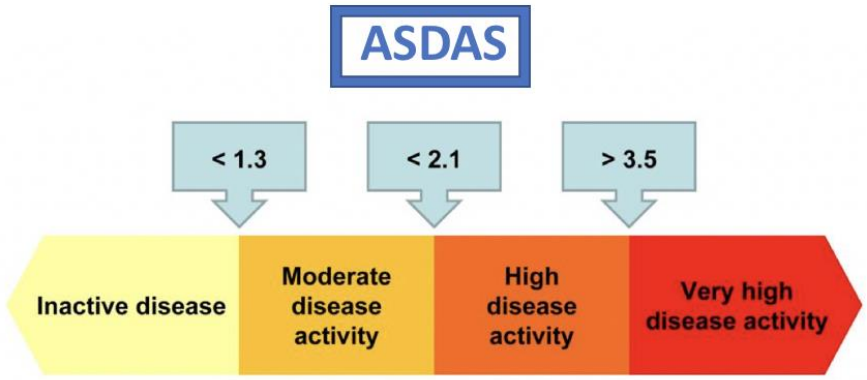
Absence of objective inflammation eg CRP/ MRI

Prevention of structural damage

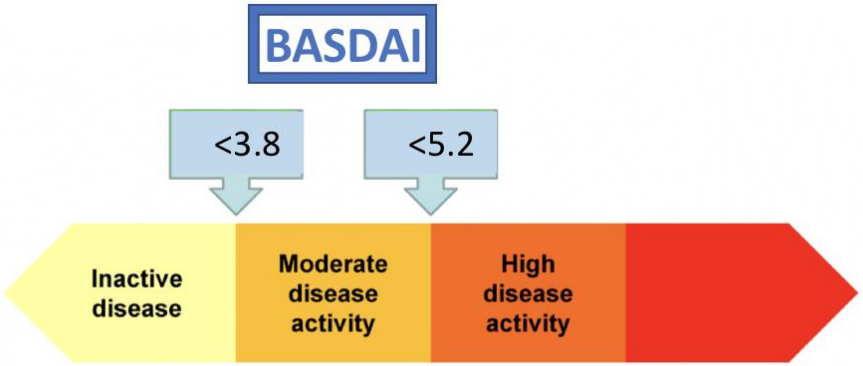
Reaching normal function

Remission of EAMs

Definitions of remission



Machado P et al. Ann Rheum Dis 2011;70:47-53 (with permission)



Godfrin-Valnet et al, Evaluation of spondylarthritis activity by patients and physicians: ASDAS, BASDAI, PASS, and flares in 200 patients. 394 M. Joint Bone Spine 80 (2013) 393–398

BASDAI Remission

- BASDAI <1

ASAS PR

- Patient global
- Spinal pain
- Function (BASFI)
- Inflammation (Q5/6 BASDAI).

All 4 domains is <2 on a scale between 0 and 10

Trajectories of disease activity in early axSpA

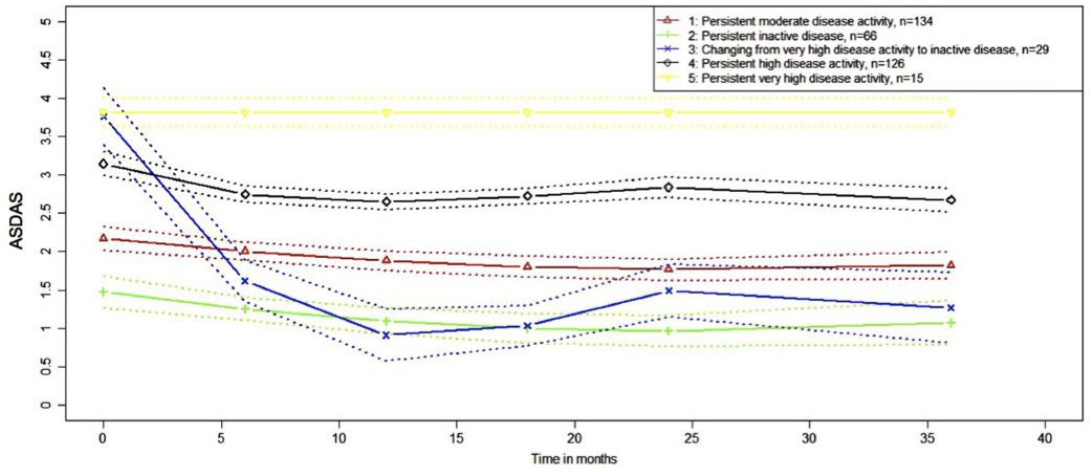


Figure 1 Trajectories of disease activity in early axial spondyloarthritis according to the group-based trajectory model technique. ASDAS, Ankylosing Spondylitis Disease Activity Score.

Molto A, et al. Ann Rheum Dis 2016;0:1–6. doi:10.1136/annrheumdis-2016-209785

Table 2 Characteristics associated with trajectories in early axial spondyloarthritis (multinomial logit regression)*

	Trajectory 2† 'Inactive disease' n=66 OR (95% CI)	Trajectory 3 'Changing disease activity' n=29 OR (95% CI)	Trajectory 4 'High disease activity' n=126 OR (95% CI)	Trajectory 5 'Very high disease activity' n=15 OR (95% CI)
Gender (male)‡	1.4 (0.6 to 3.0)	**7.1 (1.6 to 32.2)**	0.8 (0.4 to 1.2)	0.4 (0.1 to 2.0)
Education (university)	0.9 (0.3 to 2.7)	**9.4 (1.4 to 63.4)**	0.5 (0.2 to 1.2)	0.4 (0.1 to 2.2)
White-collar job (vs blue-collar job)	**2.6 (1.0 to 6.7)**	1.1 (0.3 to 5.0)	0.7 (0.3 to 1.5)	0.2 (0.0 to 1.5)
Symptoms duration (years)	**0.5 (0.3 to 0.7)**	0.9 (0.4 to 1.8)	0.9 (0.6 to 1.3)	0.8 (0.4 to 1.8)
History of peripheral arthritis	0.9 (0.4 to 2.2)	**6.2 (1.3 to 31.3)**	1.2 (0.6 to 2.4)	10.2 (1.0 to 106.5)
BASFI	1.0 (0.9 to 1.0)	1.1 (0.9 to 1.0)	**1.0 (1.0 to 1.1)**	1.0 (1.0 to 1.1)

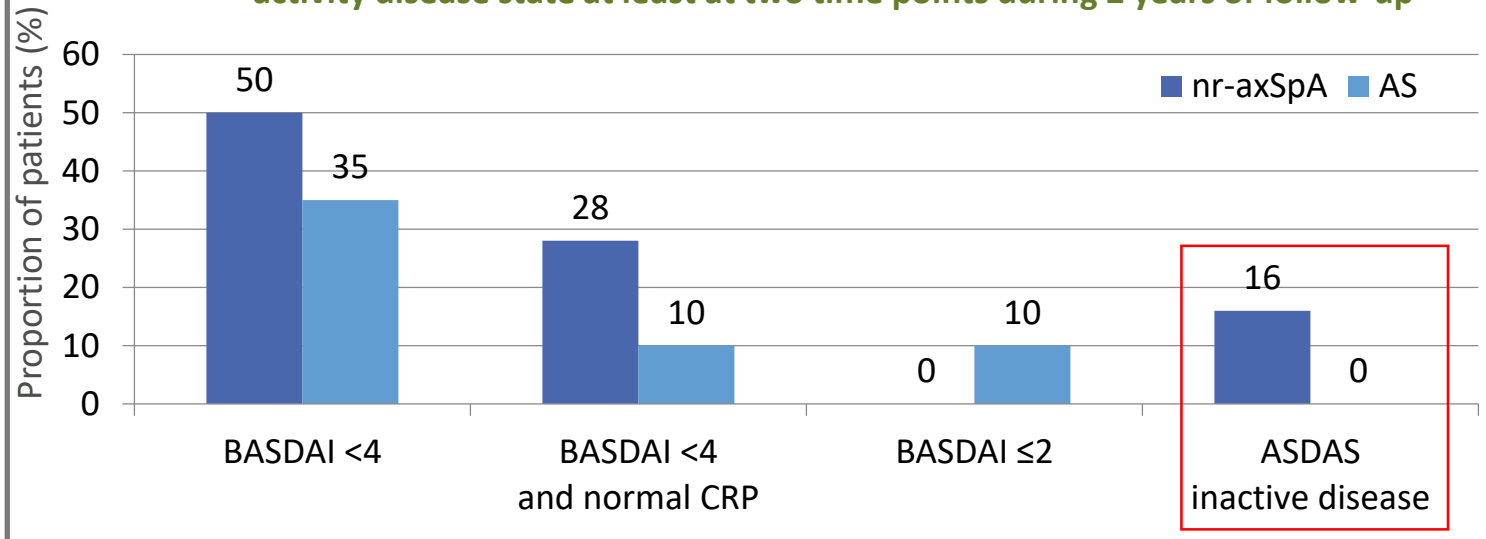
*Only variables independently associated with at least one trajectory are represented here.
†Trajectory 1 'Moderate disease activity' was the reference trajectory.
‡Statistically significant results are highlighted in bold.
BASFI, Bath Ankylosing Spondylitis Functional Index.

Achieving remission spontaneously over two year follow-up in active patients with non-radiographic axial spondyloarthritis in comparison to ankylosing spondylitis not treated with TNF blockers

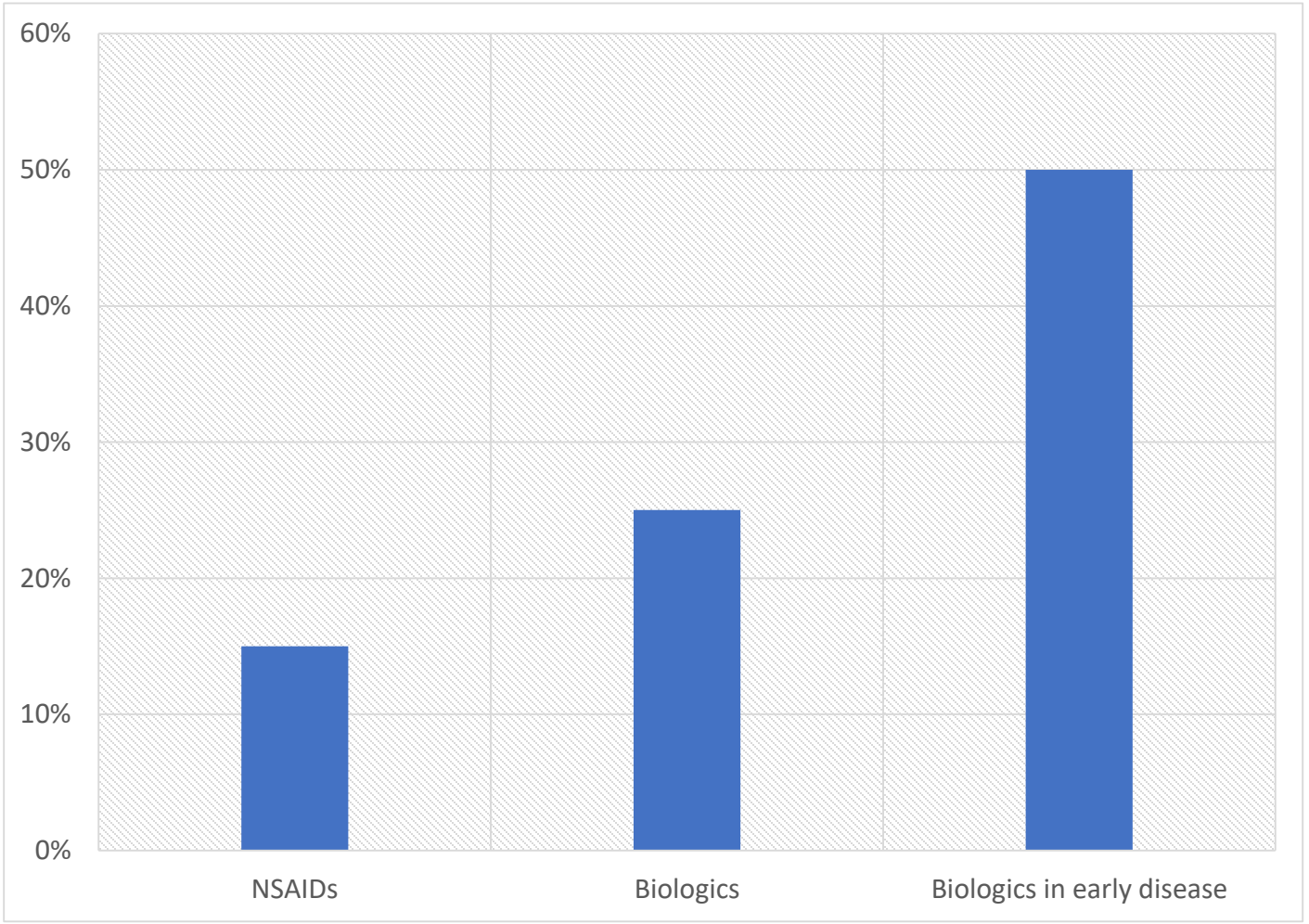
Poddubnyy *et al.* ICS 2014. Poster P88

- **Method:**
- n=210 patients with early axSpA and n=95 patients with nr-axSpA from the GESPIC trial were evaluated at baseline and every 6 months thereafter until 2 years
- Rates of remission/low disease activity states over 2 years without anti-TNF treatment were assessed
- **Results:**
- A small proportion of patients (<20%) with nr-axSpA and AS achieved remission over 2 years of follow-up without anti-TNF treatment

Proportions of patients with high disease activity at baseline who achieved a low disease activity disease state at least at two time points during 2 years of follow-up



Achieving clinical remission with medications in axSpA



Anderson JJ, Baron G, van der Heijde D, *et al.* Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. *Arthritis Rheum* 2001;**44**:1876–86.

van der Heijde D, Dijkmans B, Geusens P, *et al*. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005;**52**:582–91.

Song IH, Hermann K, Haibel H, *et al.* Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. *Ann Rheum Dis* 2011;**70**:590–6.

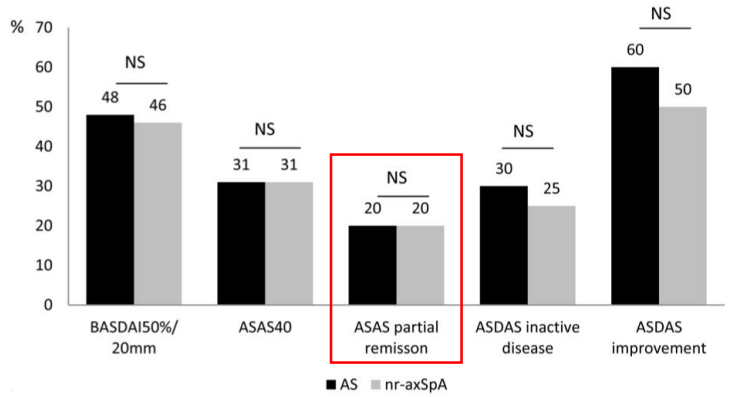
Achieving clinical remission biologics in axSpA - clinical trials

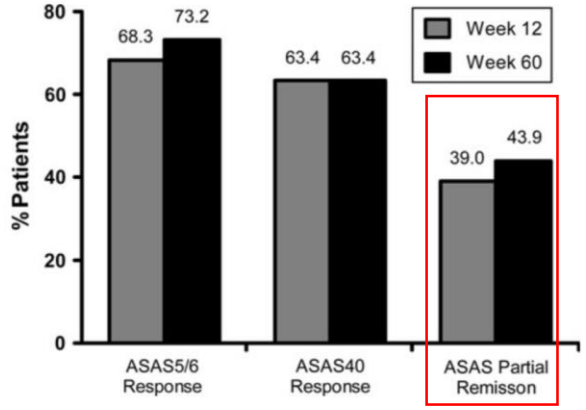
Glintborg et al. Ankylosing Spondylitis versus Nonradiographic Axial Spondyloarthritis: Comparison of Tumor Necrosis Factor Inhibitor Effectiveness and Effect of HLA-B27 Status. An Observational Cohort Study from the Nationwide DANBIO Registry. J Rheum 2017:44:1

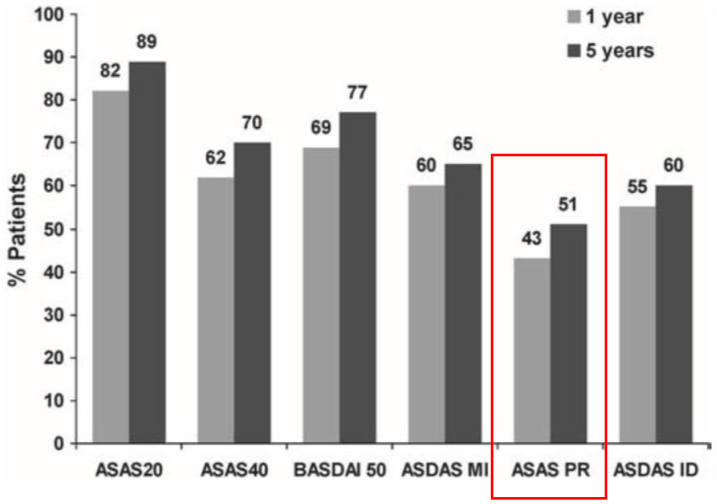
Kobayashi et al. A multicenter, open-label, efficacy, pharmacokinetic, and safety study of adalimumab in Japanese patients with ankylosing spondylitis
Mod Rheumatol (2012) 22:589–597

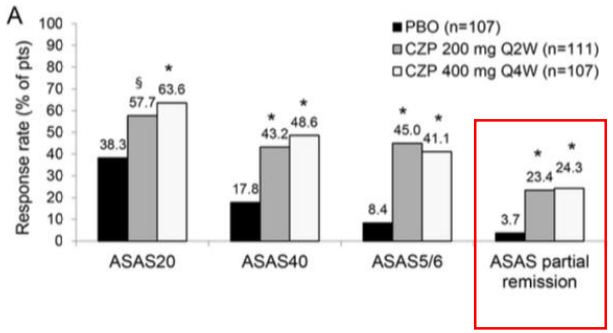
Sieper et al. Early response to adalimumab predicts long-term remission through 5 years of treatment in patients with ankylosing spondylitis *Ann Rheum Dis* 2012;**71**:700–706. doi:10.1136/annrheumdis-2011-200358

Landewe et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double- blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis 2014;73:39–47. doi:10.1136/annrheumdis-2013-204231









Predictors of achieving clinical remission biologics in axSpA - clinical trials

Perrotta et al. Predictive factors for partial remission according to the Ankylosing Spondylitis Assessment Study working group in patients with ankylosing spondylitis treated with anti-TNFα drugs
Reumatismo, 2014; 66 (3): 208-214

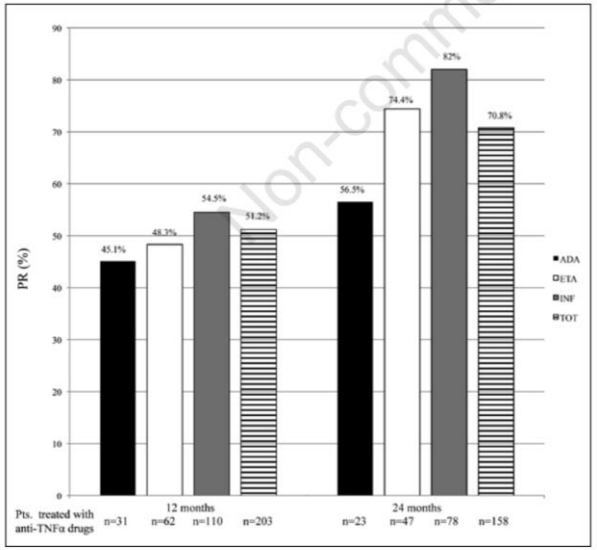


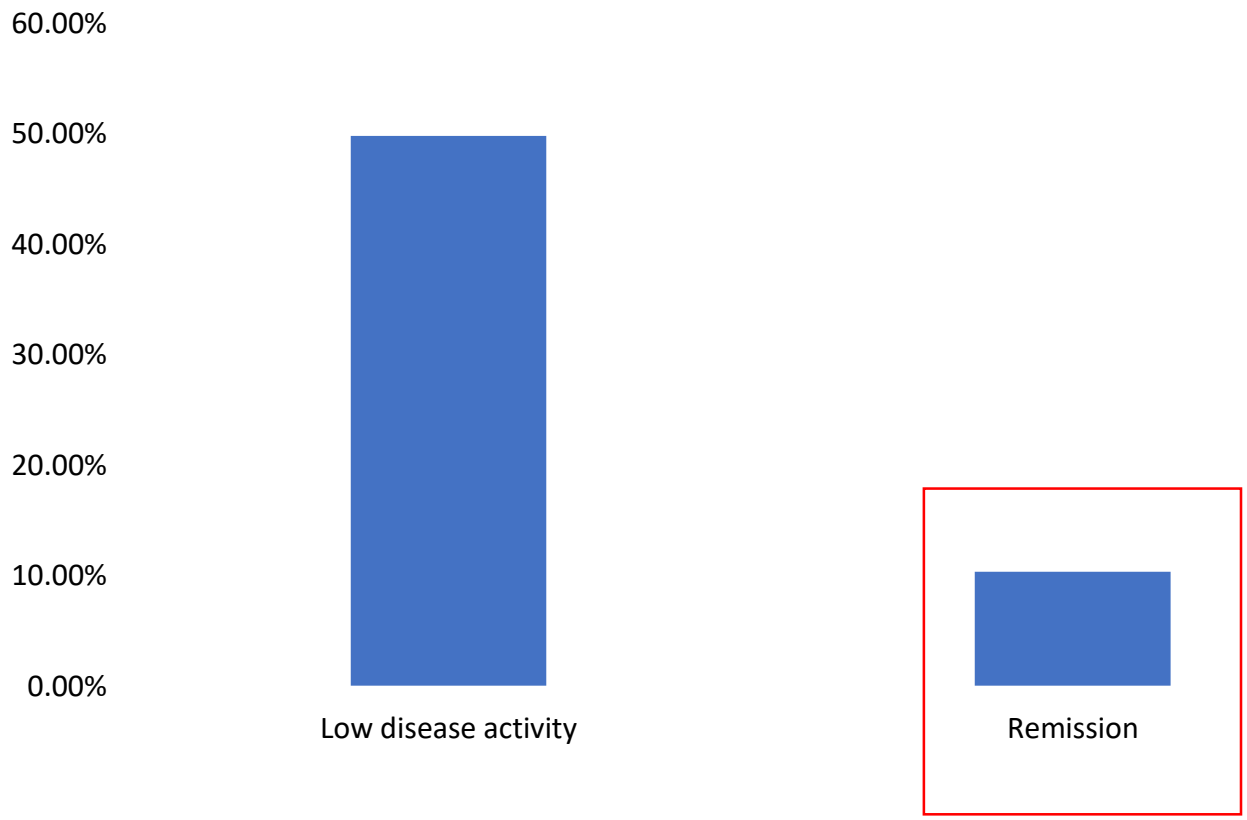
Figure 1 - Partial remission rates in ankylosing spondylitis patients receiving anti-TNFα treatment at 12 (n=203) and 24 (n=158) months.

Table II - Odds ratio (OR) and 95% confidence intervals (CI) of partial remission response in ankylosing spondylitis patients treated with ADA, ETA and INF at 12 and 24 months of follow-up.

		12 months Odds ratio (CI 95%)	P	24 months Odds ratio (CI 95%)	P
Gender	Male vs female	2.05 (1.09-3.84)	0.02	1.3 (0.60-3.04)	n.s.
Age (years)	≤34 vs >34 - ≤43	2.01 (0.78-5.18)	n.s.	2.16 (0.79-5.92)	n.s.
	≤34 vs >43 - <54	1.49 (0.65-3.40)	n.s.	1.22 (0.42-3.50)	n.s.
	≤34 vs ≥54	2.01 (0.90-4.47)	n.s.	2.44 (0.94-6.30)	n.s.
Disease duration (months)	≤36 vs >36 - ≤96	0.76 (0.34-1.65)	n.s.	1.85 (0.58-5.87)	n.s.
	≤36 vs >96 - <189	0.81 (0.35-1.84)	n.s.	2.08 (0.62-6.99)	n.s.
	≤36 vs ≥189	1.58 (0.73-3.41)	n.s.	5 (1.59-15.6)	0.005
HLA-B27	Absence vs presence	0.86 (0.46-1.63)	n.s.	1.31 (0.57-2.98)	n.s.
CRP (mg/dL)	≥2 vs >0.8 - ≤1.5	0.82 (0.39-1.70)	n.s.	1.19 (0.48-2.93)	n.s.
	≥2 vs >1.5 - <2	1.69 (0.65-4.42)	n.s.	2.38 (0.73-7.83)	n.s.
	≥2 vs ≤0.8	2.44 (1.21-4.93)	0.03	3.39 (1.43-8.04)	0.005
ESR (mm/h)	≥45 vs >17 - ≤30	1.46 (0.66-3.25)	n.s.	1.47 (0.49-4.33)	n.s.
	≥45 vs >30- <45	1.96 (0.88-4.35)	n.s.	2.38 (0.86-2.53)	n.s.
	≥45 vs ≤17	1.63 (0.73-3.62)	n.s.	3.06 (1.14-8.15)	0.02
BASDAI	≤4.8 vs >4.8 - ≤5.9	1.25 (0.55-2.79)	n.s.	0.8 (0.27-2.31)	n.s.
	≤4.8 vs >5.9 - <6.5	1.36 (0.60-3.06)	n.s.	0.77 (0.19-2.56)	n.s.
	≤4.8 vs ≥6.5	2.08 (0.93-4.64)	n.s.	2.17 (0.84-5.58)	n.s.
BASMI	≤2 vs >2 - ≤3	1.65 (0.65-3.71)	n.s.	2.3 (0.78-4.70)	n.s.
	≤2 vs >3 - <6	1.64 (0.83-3.21)	n.s.	1.59 (0.65-3.24)	n.s.
	≤2 vs ≥6	3.44 (1.28-9.11)	0.01	3.06 (0.89-10.5)	n.s.
BASFI	≤4.5 vs >4.5 - ≤5.5	0.84 (0.41-1.75)	n.s.	0.48 (0.19-1.23)	n.s.
	≤4.5 vs >5.5 - <6.5	0.65 (0.29-1.44)	n.s.	0.40 (0.14-1.09)	n.s.
	≤4.5 vs ≥6.5	1.32 (0.64-2.70)	n.s.	0.88 (0.38-2.70)	n.s.
Sacroiliitis (grade IV)	Absence vs presence	1.39 (0.76-2.56)	n.s.	1.42 (0.67-2.97)	n.s.
Peripheral arthritis	Absence vs presence	1.47 (0.84-1.55)	n.s.	0.63 (0.32-1.25)	n.s.
Psoriasis	Absence vs presence	2.46 (0.98-6.16)	0.05	2.18 (0.79-6)	n.s.
IBD	Absence vs presence	0.7 (0.29-1.71)	n.s.	0.75 (0.25-2.23)	n.s.
Uveitis	Absence vs presence	1.45 (0.7-2.46)	n.s.	1.95 (0.82-4.58)	n.s.

Achieving clinical remission biologics in axSpA - real world experience

Yahya F, Gaffney K, Hamilton L, Lonsdale E, Leeder J, Brooksby A, Cavill C, Berry-Jenkins J, Boyle C, Bond D, **Sengupta R**; BRITSpA. Tumour necrosis factor inhibitor survival and predictors of response in axial spondyloarthritis-findings from a United Kingdom cohort. Rheumatology 2018. 57(4); 619-624



Predictors of Remission

Non smoker

Remission in axSpA

Clinical remission

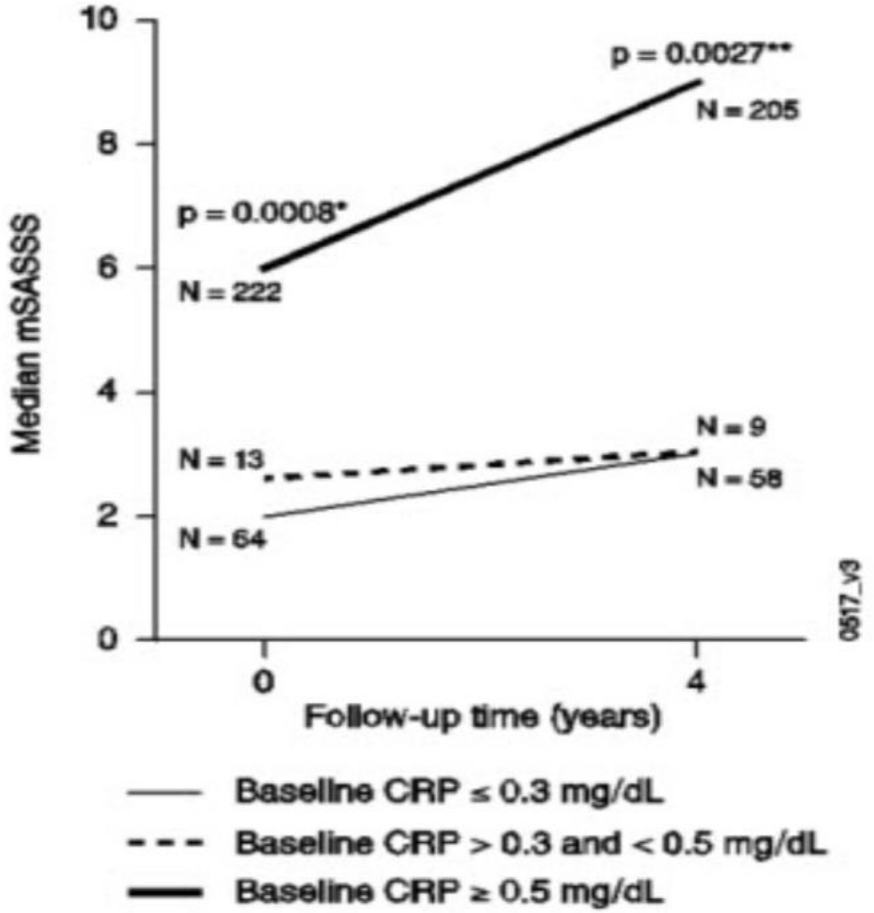
Absence of objective inflammation eg CRP/ MRI

Prevention of structural damage

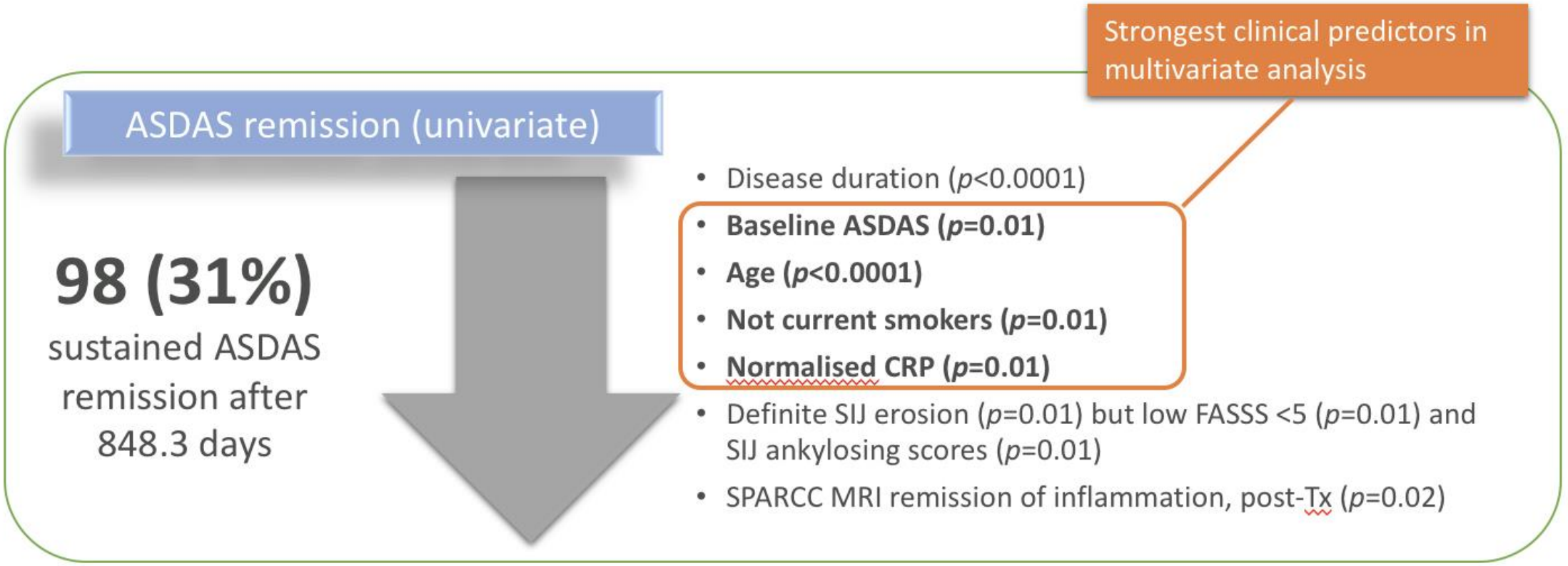
Reaching normal function

Remission of EAMs

CRP and radiographic progression



Braun et al. EULAR 2016

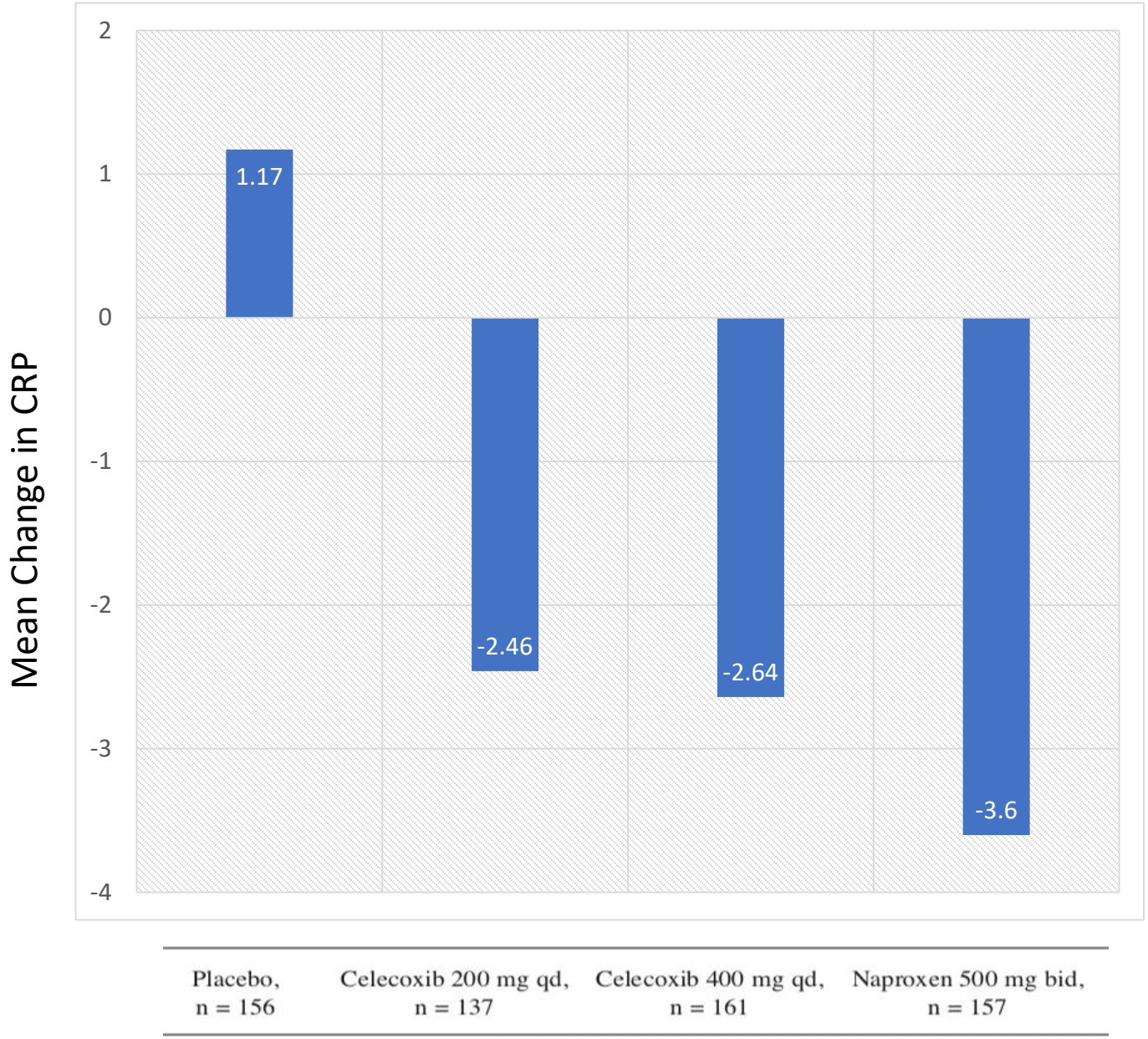


Normal CRP is associated with clinical remission in ax SpA patients treated with biologics

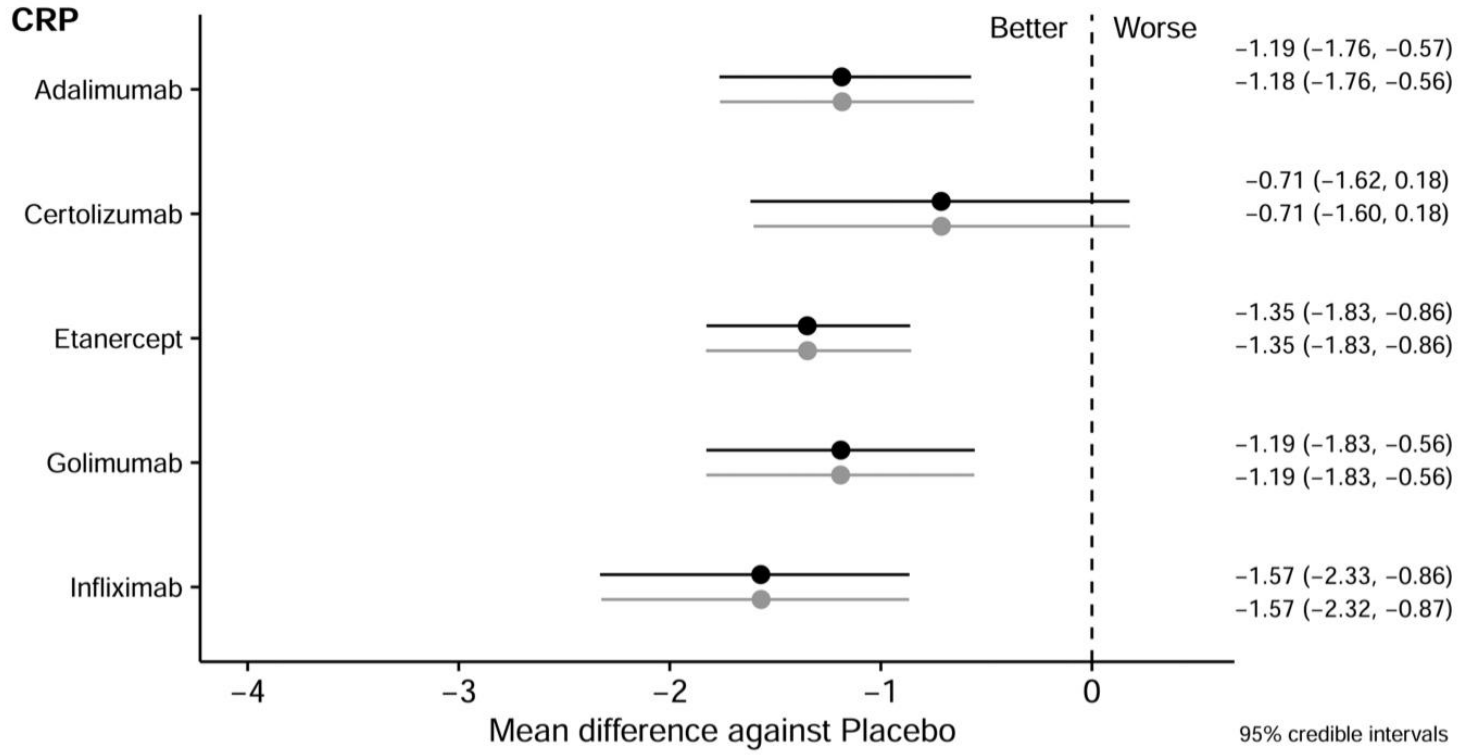
Pederson *et al*. 10th International Congress on Spondyloarthritides. 2016

CRP reduction with celecoxib and naproxen over 12 weeks

Barkhuizen et al. Celecoxib Is Efficacious and Well Tolerated in Treating signs and Symptoms of Ankylosing Spondylitis. *The Journal of Rheumatology 2006; 33:9*



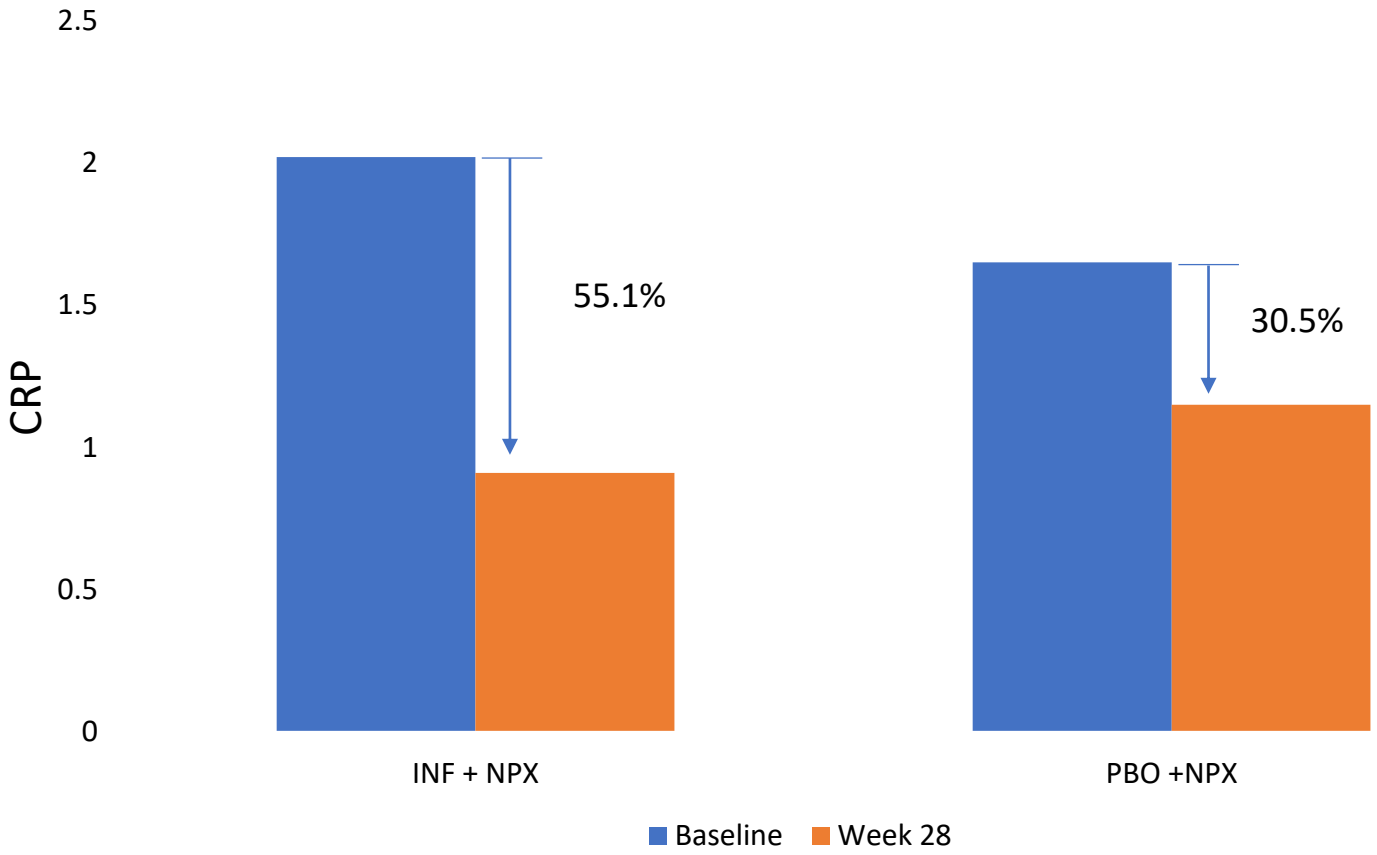
CRP reduction with biologics



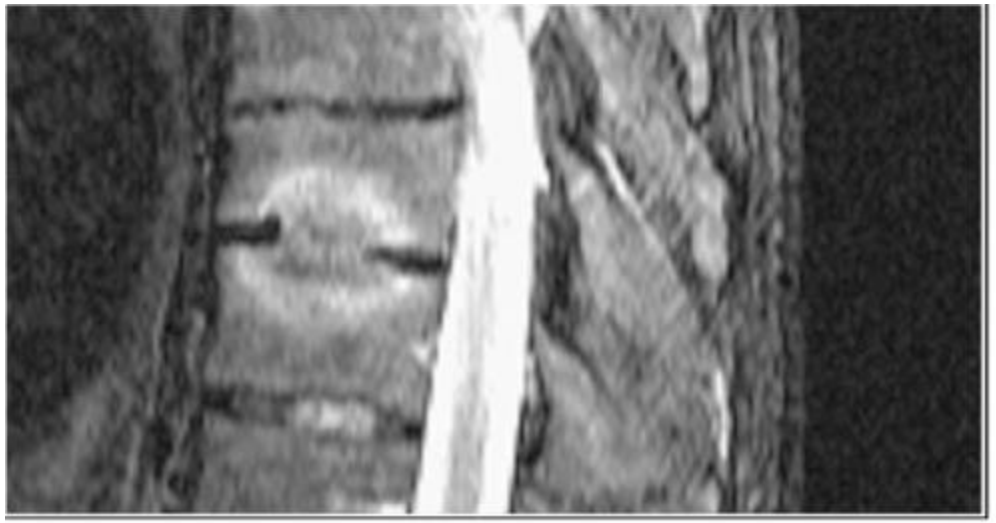
Wang et al. Comparative Efficacy of Tumor Necrosis Factor-α Inhibitors in Ankylosing Spondylitis: A Systematic Review and Bayesian Network Metaanalysis. J Rheumatol 2018;45:481-490

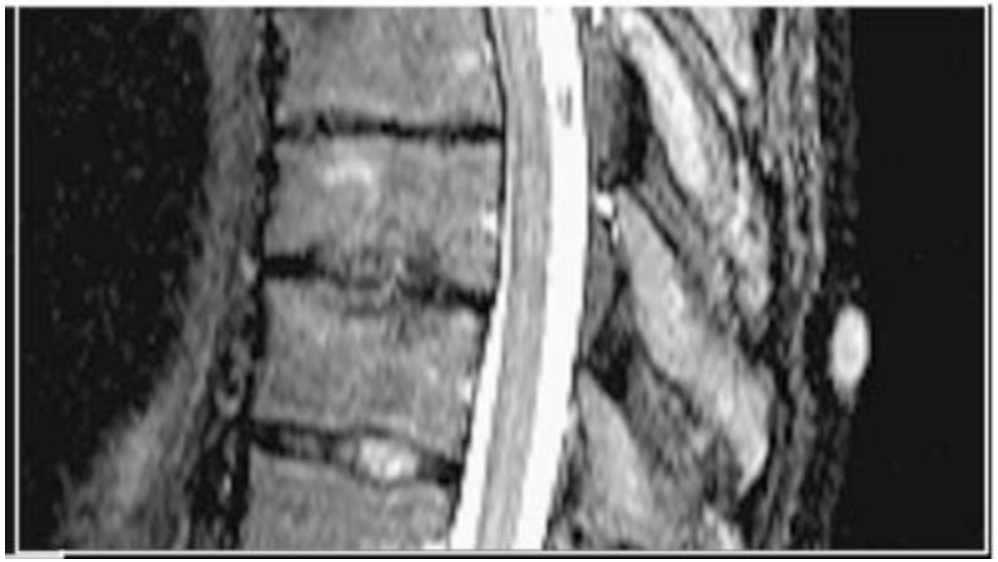
CRP reduction with NSAIDs and biologics

Sieper et al. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1
Ann Rheum Dis 2013;0:1–7. doi:10.1136/annrheumdis-2012-203201



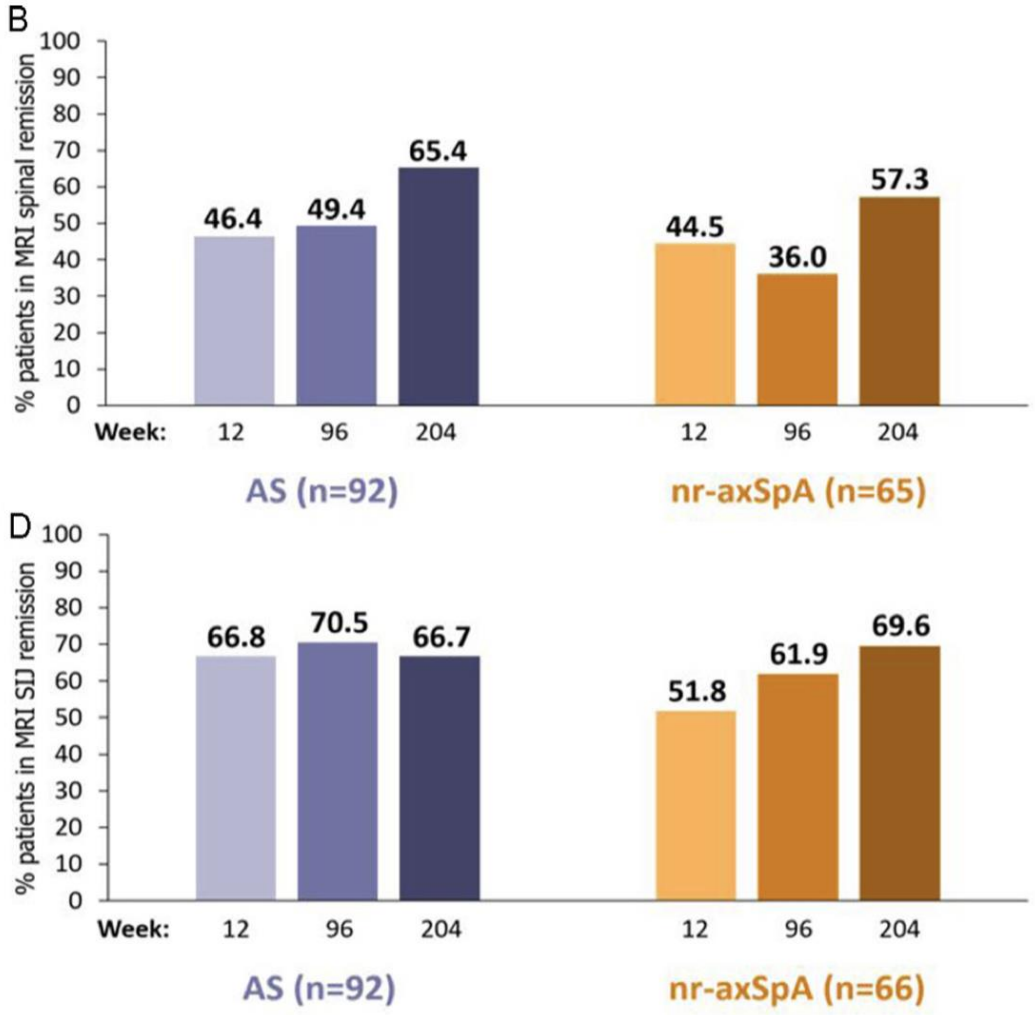
Improvement of MRI lesions with anti TNF treatment





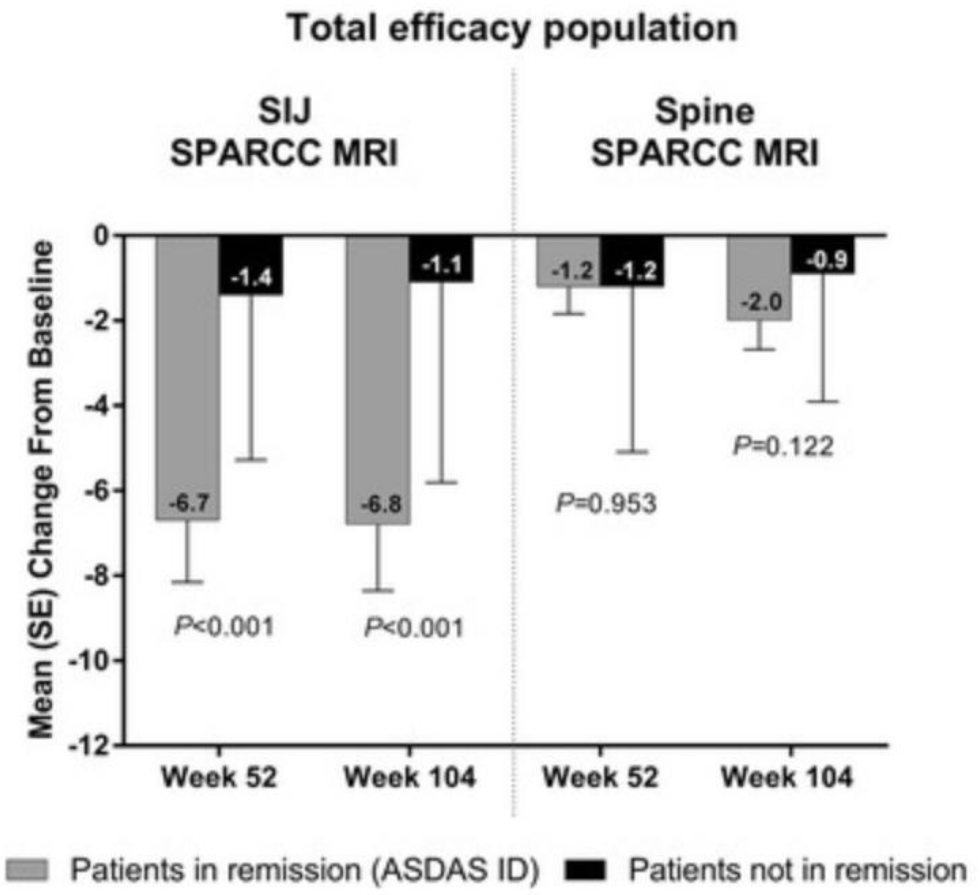
Achievement of MRI remission with biologics

Van der Heijde et al. Limited radiographic progression and sustained reductions in MRI inflammation in patients with axial spondyloarthritis: 4-year imaging outcomes from the RAPID-axSpA phase III randomised trial. Ann Rheum Dis 2018;0:1–7. doi:10.1136/annrheumdis-2017-212377



MRI imaging results to week 204. (B) percentage of patients in MRI spinal remission (Berlin score ≤2) to week 204 (missing at random (MAR)) in the subgroup of patients with MRI spinal inflammation at baseline (Berlin score >2), (D) percentage of patients in MRI SIJ remission (SPARCC score <2) to week 204 (MAR)

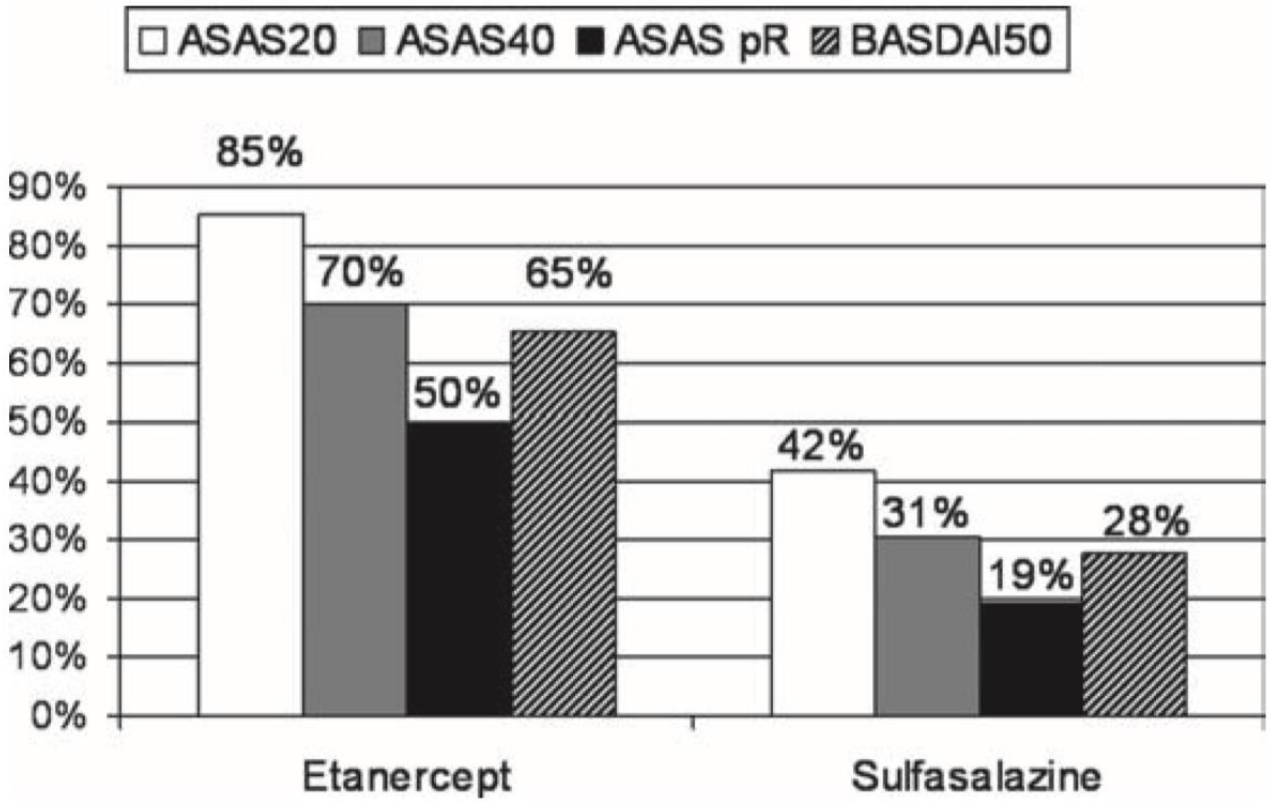
MRI remission more likely with patients in clinical remission



Van der Heijde et al. Clinical and MRI remission in patients with nonradiographic axial spondyloarthritis who received long-term open-label adalimumab treatment: 3-year results of the ABILITY-1 trial. Arthritis Research & Therapy (2018) 20:61

Patients who achieved ASDAS ID at year 2, 44–68% also had MRI remission.

Persistence of MRI inflammation despite clinical remission



50% of patients with axial SpA reached clinical remission after 1 year of treatment with etanercept

and

only 15% became completely free of any inflammation on MRI

Song IH, Hermann K, Haibel H, *et al.* Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. *Ann Rheum Dis* 2011;**70**:590–6.

Does remission make a difference in axSpA?

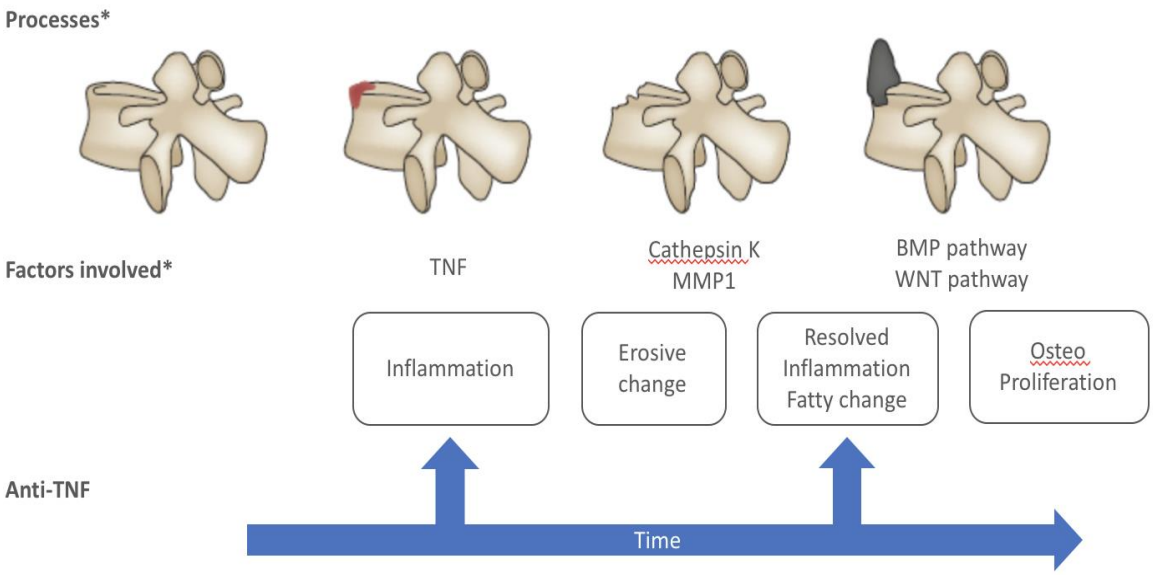
Clinical remission

Absence of objective inflammation eg CRP/ MRI

Prevention of structural damage

Reaching normal function

Remission of EAMs

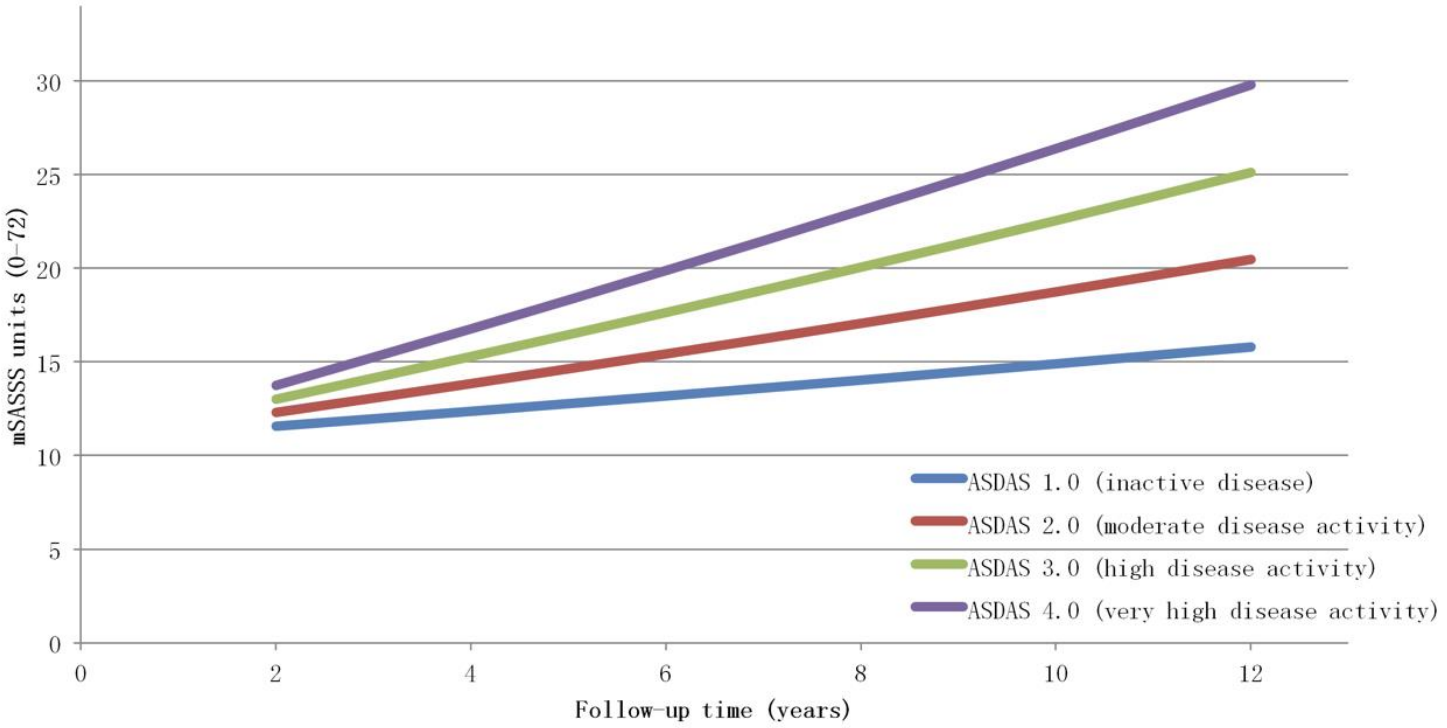


- No prospective studies looking at **clinical remission, serological** and **MRI remission** on radiographic progression
- Some retrospective data exists

Remission and radiographic progression

Tam LS et al. Nat Rev Rheum 2010;6:339–405; Sieper J et al. Arthritis Rheum 2008;58:649–56

Is absolute remission required over low disease activity to prevent radiographic progression?



Ramiro S, et al. *Ann Rheum Dis.* 2014;73:1455–61.
ASDAS, Ankylosing Spondylitis Disease Activity Score; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score

Does remission make a difference in axSpA?

Clinical remission

Absence of objective inflammation eg CRP/ MRI

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Remission of EAMs

The Bath Ankylosing Spondylitis Functional Index (BASFI) effectively measures treatment response in AS patients at all stages of disease duration

Table 1: Characteristics of the study cohort

Statistic	Value
n	220
% male	78.2
Mean age, years (± s.d.)	48.3 (±12.04)
Mean age at symptom onset, years (± s.d.)	20.8 (±7.91)
Mean disease duration since symptom onset, years (± s.d.)	27.5 (±12.46)

Table 2. Changes in BASFI score associated with a 2-week inpatient physiotherapy course

Disease duration (yrs)	n	Mean BASFI		Change	% change	Effect size
		Start	End			
Full sample	220	4.56	3.29	1.27	27.9	0.564
<10	23	3.54	2.47	1.07	30.2	0.540
10.0-19.9	36	4.20	3.02	1.18	28.1	0.460
20.0-29.9	59	4.59	3.30	1.29	28.1	0.586
≥30.0	102	4.90	3.57	1.33	27.1	0.622

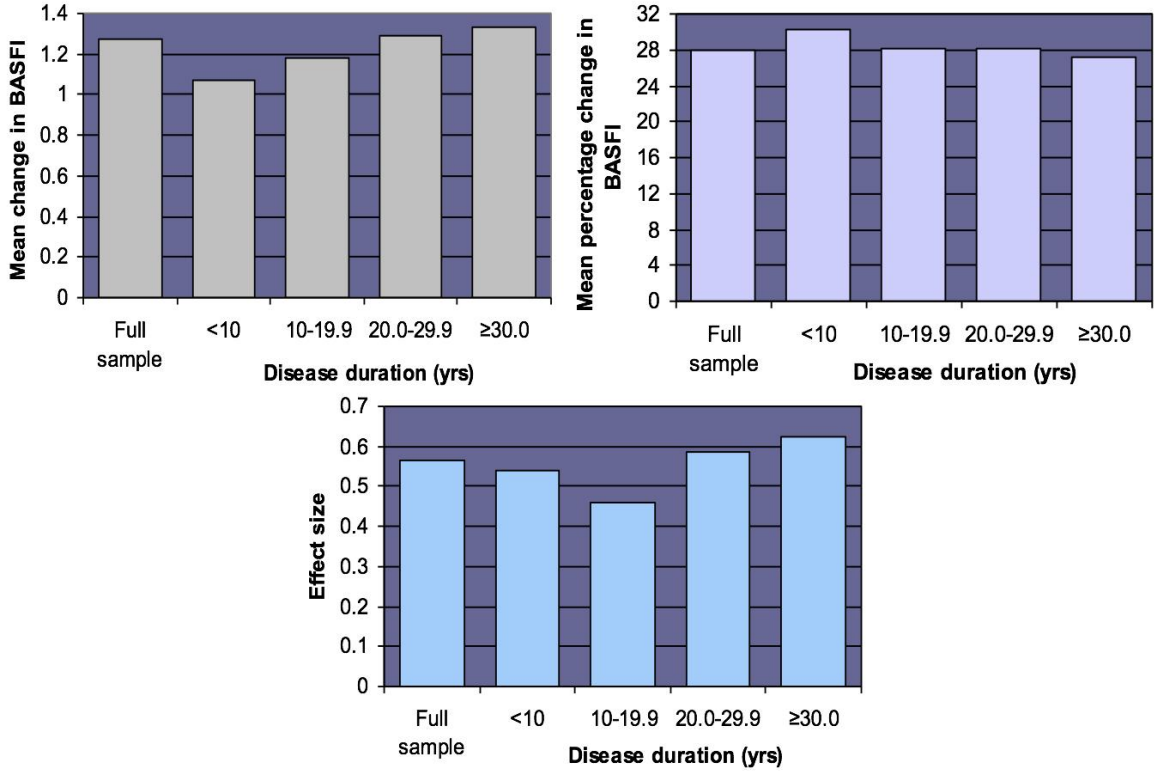
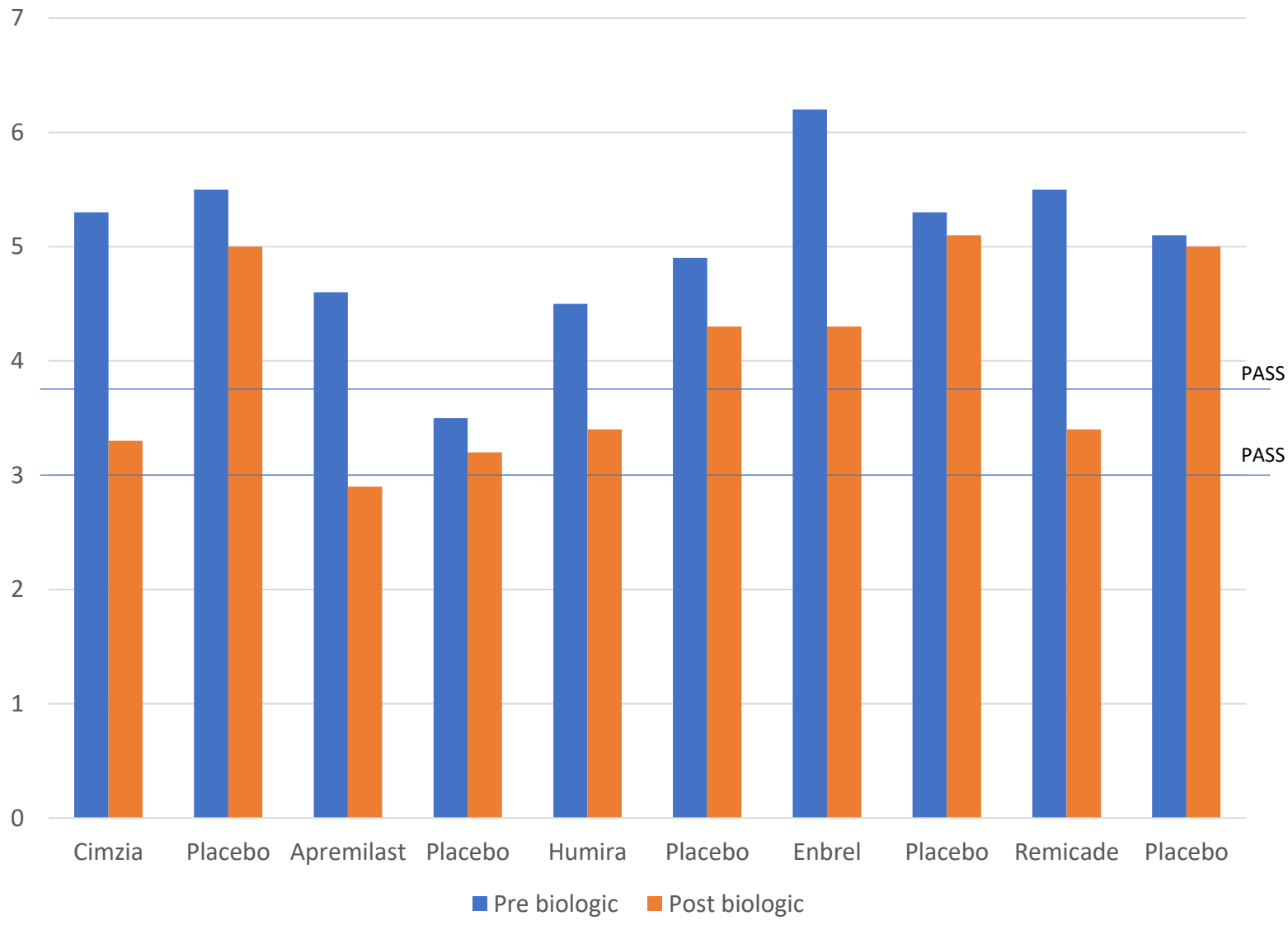


Figure 1: Mean BASFI change, mean percentage BASFI change and effect size for groups of differing disease duration

Bath SpA Cohort

Sengupta R, Pomeroy E, Mogg R, Richardson J, Gay L, Stone MA. The Bath Ankylosing Spondylitis Functional Index (BASFI) effectively measures treatment response in AS patients at all stages of disease duration. Rheumatology 2008; 47(Suppl. 2): 261

BASFI pre and post biologics with MCID



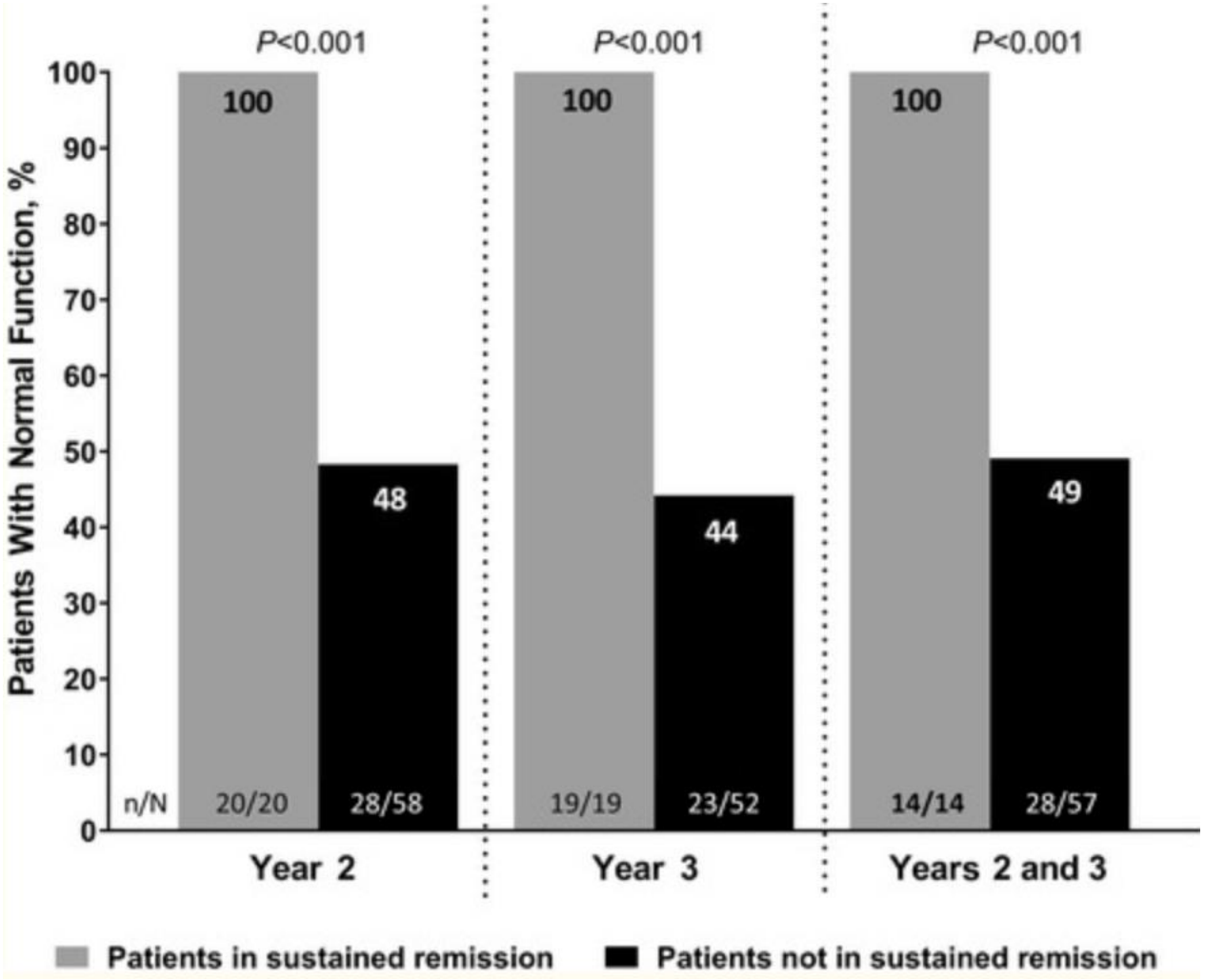
MCID BASFI 0.7

MCII BASFI 0.6

PASS BASFI 3.8

The relationship between physical function and clinical remission

Van der Heijde et al. Clinical and MRI remission in patients with nonradiographic axial spondyloarthritis who received long-term open-label adalimumab treatment: 3-year results of the ABILITY-1 trial. Arthritis Research & Therapy (2018) 20:61



Normal/patient acceptable physical function was defined as BASFI ≤ 3.

Does remission make a difference in axSpA?

Effects of BASDAI remission on patient reported outcomes

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	BASDAI remission	BASDAI>1	
ASQOL (0-18)	1.58 (0.35)	7.4 (5.15)	p<0.003
EQ5D	80.75 (16.56)	60.91 (20.72)	p<0.003
BASFI	12.76 (14.71)	25.64 (1.05)	p<0.003
BASMI	2.57 (2.04)	3.55 (2.24)	p<0.003
FACIT	9.13 (5.83)	22.37 (10.96)	p<0.003

n=718

Unpublished data

EMBARK: The impact of ASDAS inactive disease on patient reported outcomes in nr-axSpA

- *Post-hoc* analyses
- Active, NSAID-resistant, nr-axSpA
- ETN 50 mg/week or PBO to Week 12, followed by ETN 50 mg/week to Week 104
- At Weeks 12 and 104, patients were grouped based on ASDAS ID vs active disease
- Changes in PROs were compared between groups in the mITT population with observed cases

	Least square means change from baseline (SE)			
	Week 12		Week 104	
Patient-reported outcome	**ASDAS Inactive disease**	**ASDAS Active disease**	**ASDAS Inactive disease**	**ASDAS Active disease**
Nocturnal back pain (0–10 VAS)	-4.1 (0.3) p≤0.0001	-1.0 (0.2)	-4.6 (0.2) p≤0.0001	-2.1 (0.2)
MFI general fatigue (4–20)	-2.2 (0.4) p≤0.001	-0.5 (0.3)	-4.6 (0.4) p≤0.0001	-0.5 (0.5)
EQ-5D (0–100 VAS)	20.6 (2.5) p≤0.0001	1.9 (1.6)	26.9 (1.4) p≤0.0001	12.0 (1.9)
SF-36 PCS (0–100)	9.3 (0.8) p≤0.0001	3.0 (0.5)	13.1 (0.6) p≤0.0001	4.7 (0.9)
SF-36 MCS (0–100)	4.7 (1.2)	2.1 (0.8)	6.3 (0.9) p≤0.0001	0.5 (1.2)
AsQoL (0–18)	-3.7 (0.5) p≤0.0001	-1.3 (0.3)	-5.6 (0.3) p≤0.0001	-1.8 (0.5)
WPAI-AS absenteeism (0–100% work time missed)	-7.4 (3.4)	0.0 (2.5)	-8.8 (0.8)	-7.3 (1.4)
WPAI-AS presenteeism (0–100% work time missed)	-27.1 (3.6) p≤0.0001	-4.7 (2.6)	-28.8 (2.0) p≤0.0001	-9.5 (3.7)

Dougados M, et al. *Arthritis Rheumatol*. 2016;68(suppl10);Abstract#2779.

ASDAS, Ankylosing Spondylitis Disease Activity Score; ASQoL, ankylosing spondylitis quality of life; EQ-5D, EuroQoL 5 dimensions questionnaire; ETN, etanercept; MFI, multidimensional fatigue inventory; ID, inactive disease; mITT, modified intent to treat; NSAID, non-steroidal anti-inflammatory drug; PBO, placebo; PRO, patient-reported outcome; SE, standard error; SF-36, short form 36-item health survey; VAS, visual analogue score; WPAI-AS, work productivity and activity impairment ankylosing spondylitis

Summary

- Less than 20% of patients achieve remission without treatment
- ASAS PR reached in 20 -50% patients treated with biologics
- Predictors of clinical remission include shorter disease duration, raised inflammatory markers and normalising CRP
- MRI activity exists in patients who are in clinical remission - approx. 50%
- Around 70% patients treated with Biologics achieve MRI remission
- Retrospective data shows that clinical remission is associated with limited radiographic progression
- Functional remission is yet to be defined
- Remission is associated with a wide range of QOL outcomes