GRAPPA

Group for Research
and Assessment of Psoriasis and Psoriatic Arthritis

Sponsored by NOVARTIS

GRAPPA
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

EGYPT 2024

GRAPPA
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

Our Expectation in SpA Management.

Kurt de Vlam , MD, PhD

Department of Rheumatology,University Hospitals Leuven

Skeletal Biology and Engineering Research Center (SBE),

Dept Development and Regeneration, KULeuven, Belgium

Cairo , Egypt, 24th of May 2024

Disclosures

- Grants/Research Support: Celgene, MSD
- Speaking Engagements/Honoraria: Amgen, Pfizer, Eli Lilly, Abbvie, UCB, Novartis,
- Consulting Fees: Pfizer, Abbvie, J&J , Eli Lilly,UCB, Novartis, Amgen

- This presentation is the full property of Kurt de Vlam. All statements made are at the full responsibility of Kurt de Vlam

GRAPPA
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

Axial SpA and PsA: Resetting Our Expectation in Axial SpA and PsA Management

- Axial Spondyloarthritis
  1. the updated ASAS-EULAR recommendations
  2. Radiographic versus non radiographic axial spondyloarthritis
  3. Gender differences in ax-SpA
  4. Treatment target: Treat to Target in ax-SpA
  5. Tapering: worth the effort?
  6. Difficult to treat SpA

ASAS-EULAR recommendations for the managment of axial spondyloarthritis (2022 update)

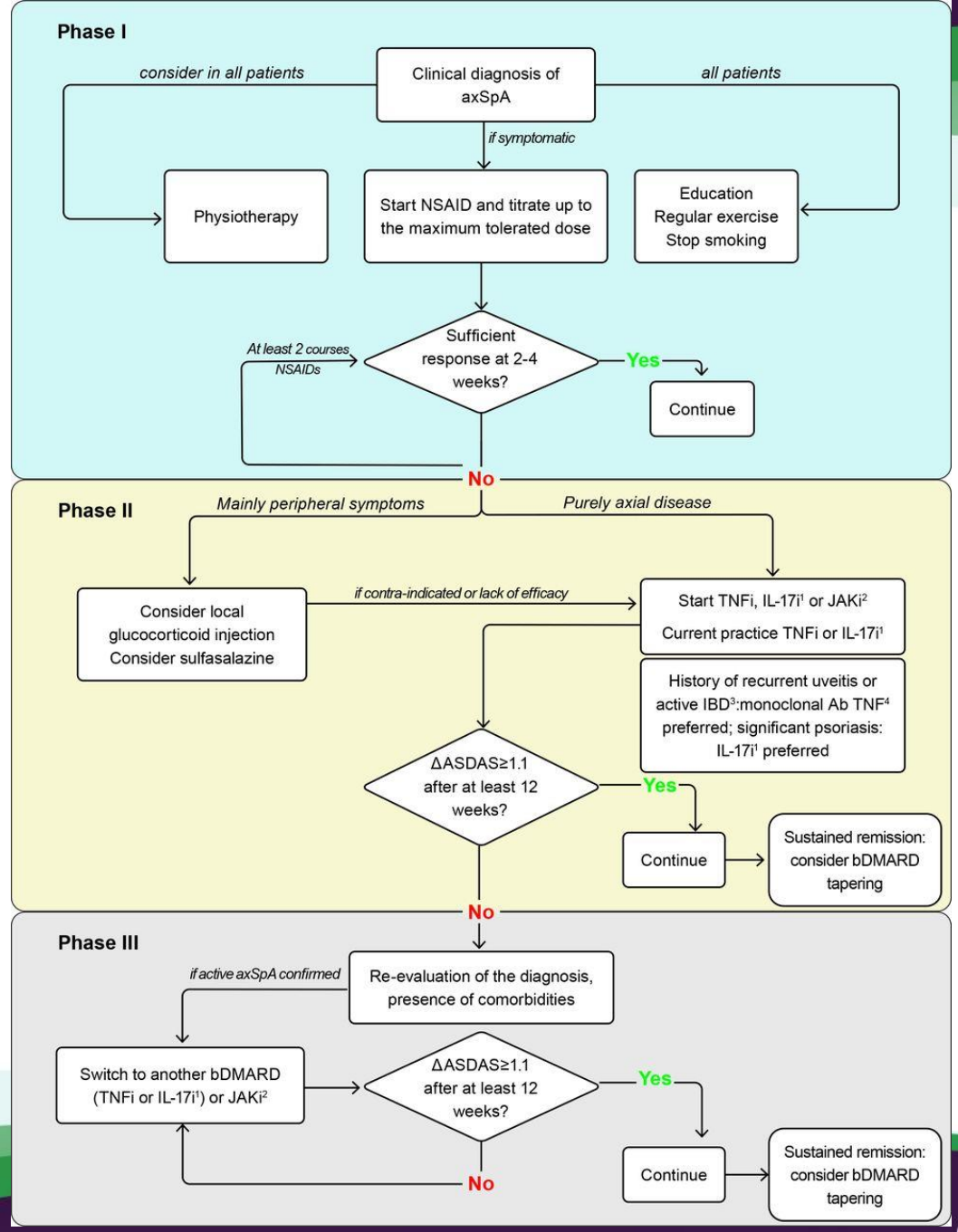
	Recommendations		LoA(0-10)	
		Levels of evidence/grade of recommendation	Mean (SD)	% with score ≥8
9	TNFi, IL-17i† or JAKi‡ should be considered in patients with persistently high disease activity despite conventional treatments current practice is to start a TNFi or IL-17i†.	1a/A	9.2 (1.2)	94
10	If there is a history of recurrent uveitis or active IBD, preference should be given to a monoclonal antibody against TNF In patients with significant psoriasis, an IL-17i† may be preferred.	2b/B (uveitis, IBD) 1a/B (psoriasis)	9.1 (1.8)	97
11	Absence of response to treatment should prompt re-evaluation of the diagnosis and consideration of the presence of comorbidities.	5/D	9.5 (0.8)	97
12	Following a first b/tsDMARD failure, switching to another bDMARD (TNFi or IL-17i†) or a JAKi‡ should be considered.	2b/B (TNFi after TNFi failure) 1b/A (IL-17i after TNFi failure) 5/D (all other switches)	9.3 (1.1)	88

Sofia Ramiro et al. Ann Rheum Dis 2023;82:19-34

9,12: updated recommendations, 10&11 new recommendations

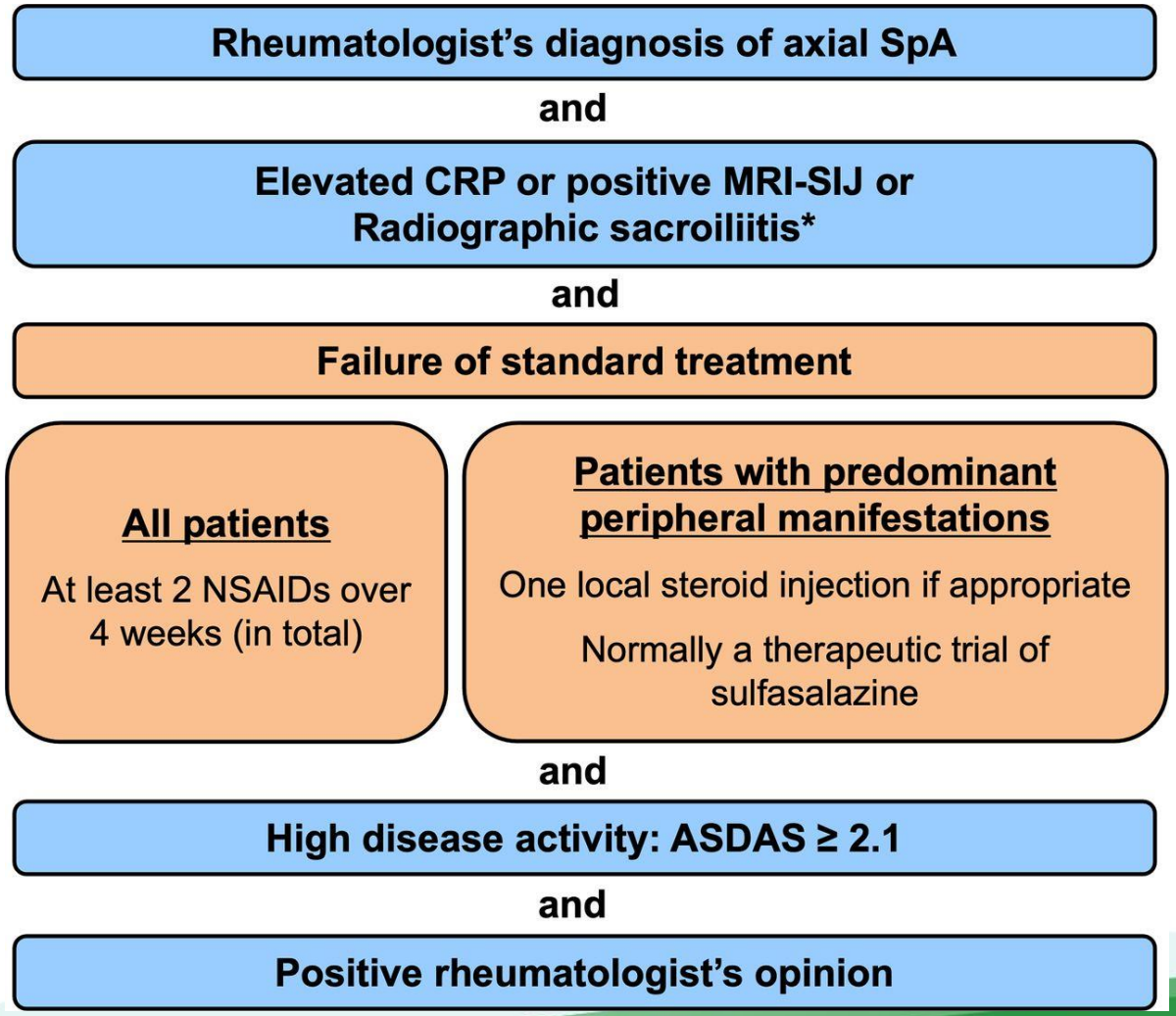
GRAPPA
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

Algorithm based on the ASAS-EULAR recommendations for the management of axial spondyloarthritis (axSpA).



Sofia Ramiro et al. Ann Rheum Dis 2023;82:19-34

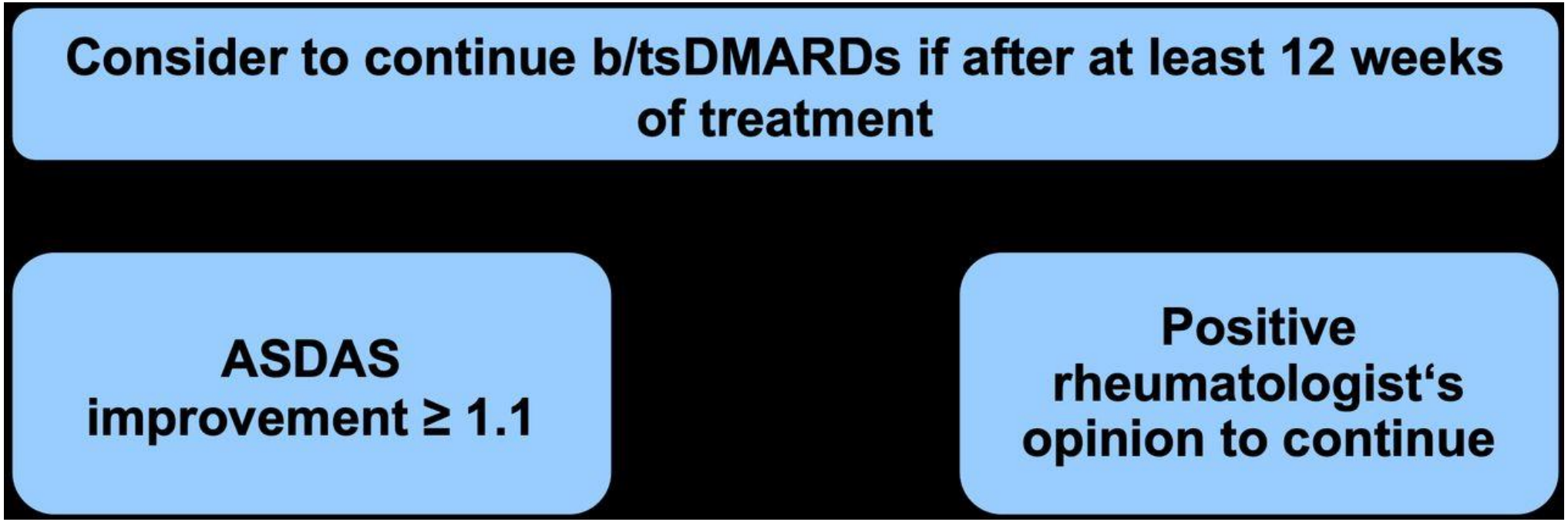
GRAPPA
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis



ASAS-EULAR recommendations for the treatment of patients with axial SpA with b/tsDMARDs.

Sofia Ramiro et al. Ann Rheum Dis 2023;82:19-34

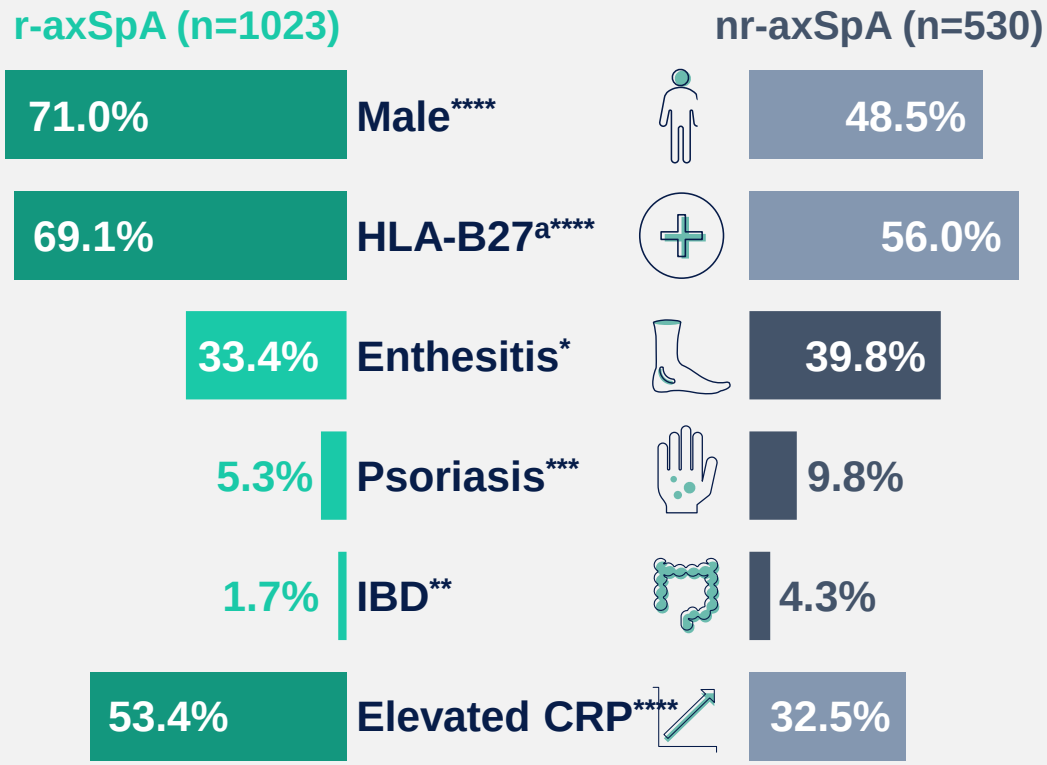
ASAS-EULAR recommendations for the continuation of b/tsDMARDs.



Sofia Ramiro et al. Ann Rheum Dis 2023;82:19-34

There are some differences between SpA features for patients with r-axSpA vs. nr-axSpA

Significantly Different



Similar between r-axSpA and nr-axSpA

- Age
- Inflammatory back pain
- Peripheral arthritis
- Dactylitis
- Uveitis
- Good response to NSAIDs
- Family history

P value for r-axSpA vs nr-axSpA: *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 aBased on patients with HLA-B27 assessed
axSpA, axial spondyloarthritis; CRP, c-reactive protein; HLA-B27, human leukocyte antigen-B27; IBD, inflammatory bowel disease; nr-axSpA, non-radiographic axSpA; r-axSpA, radiographic axSpA

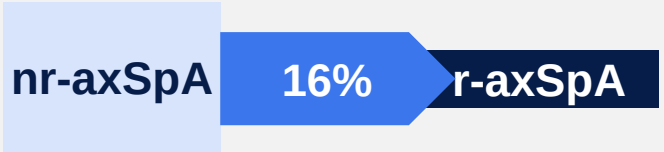
Sponsored by NOVARTIS

Adapted from: 1. Poddubnyy D, et al. Rheumatology (Oxford) 2021;doi: 10.1093/rheumatology/keab901.

Predictors of radiographic progression from nr-axSpA to r-axSpA over 5 years: the PROOF study

Patients who Progressed

- Among 246 patients with nr-axSpA who had ≥1 follow-up SIJ radiograph: **16%** (n=40) progressed from nr-axSpA to r-axSpA
- Mean time to progression: **2.4 years** (0.9-5.1 years)



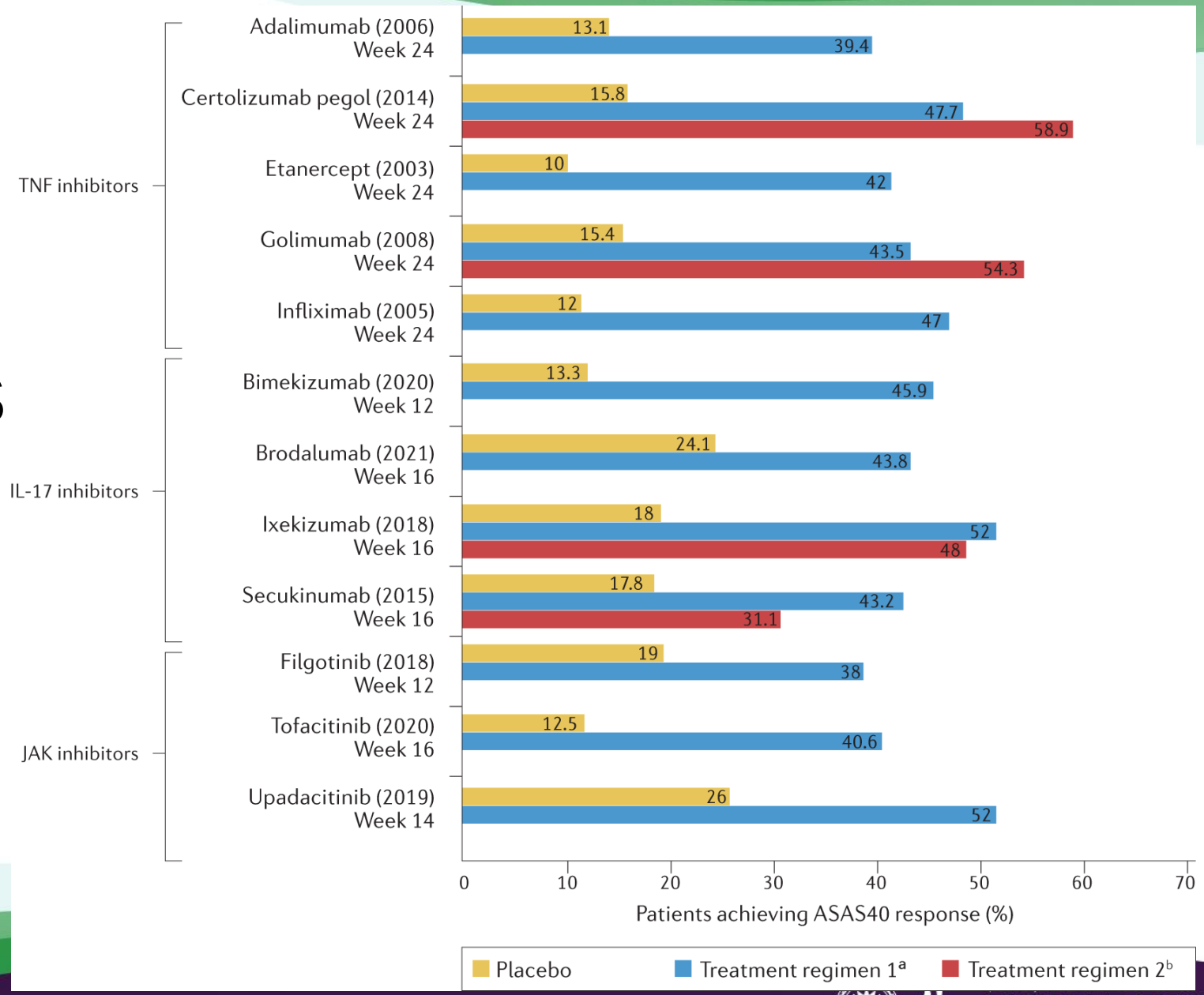
Predictors of Radiographic Progression

- Male gender
- Fulfilment of the imaging arm (i.e., the presence of sacroiliitis on MRI)
- HLA-B27 positivity
- Good response to NSAIDs

ASAS, Assessment of SpondyloArthritis international Society; HLA-B27, human leukocyte antigen B27; nr-axSpA, nonradiographic axial spondyloarthritis; r-axSpA, radiographic axial spondyloarthritis; SIJ, sacroiliac joint

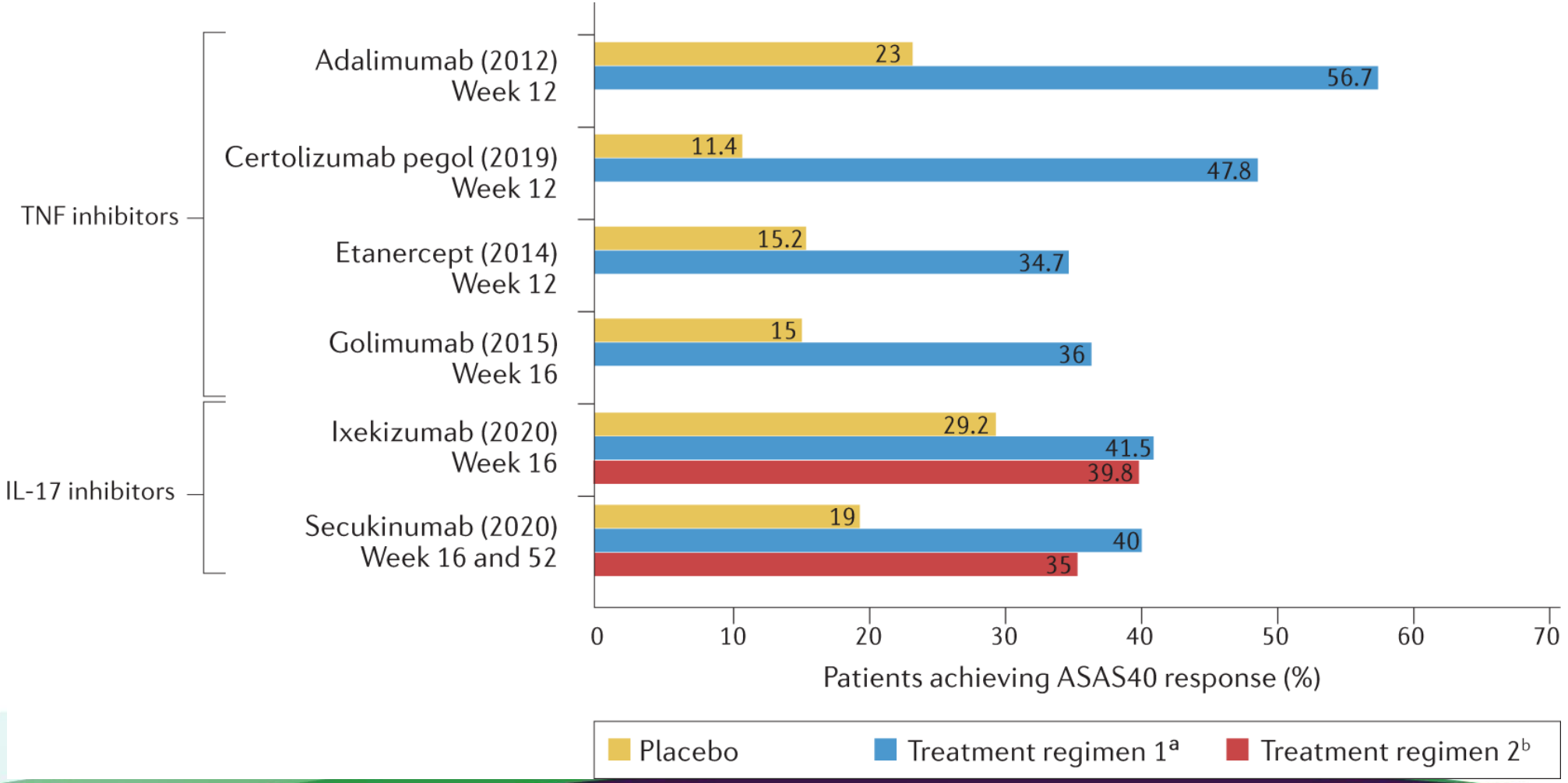
Adapted from Poddubnyy D, et al. Poster presented at EULAR 2022; 1-4Jun22, Kopenhagen (Poster 0P0149)

ASAS40 responses from clinical trials in AS



Danve, A., Deodhar, A. Treatment of axial spondyloarthritis: an update. *Nat Rev Rheumatol* **18**, 205–216 (2022).

ASAS40 responses from clinical trials in nr-axSpA

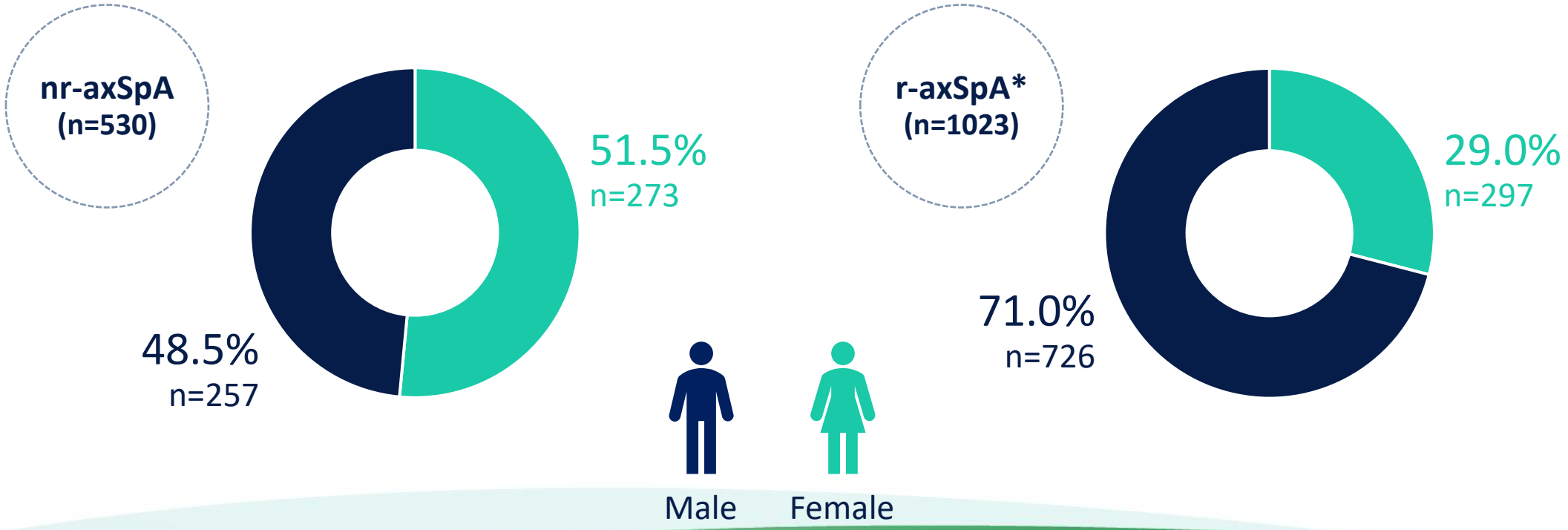


Danve, A., Deodhar, A. Treatment of axial spondyloarthritis: an update. *Nat Rev Rheumatol* **18**, 205–216 (2022).

There are sex differences in the prevalence of axSpA subtypes

nr-axSpA has a **similar prevalence** between males and females

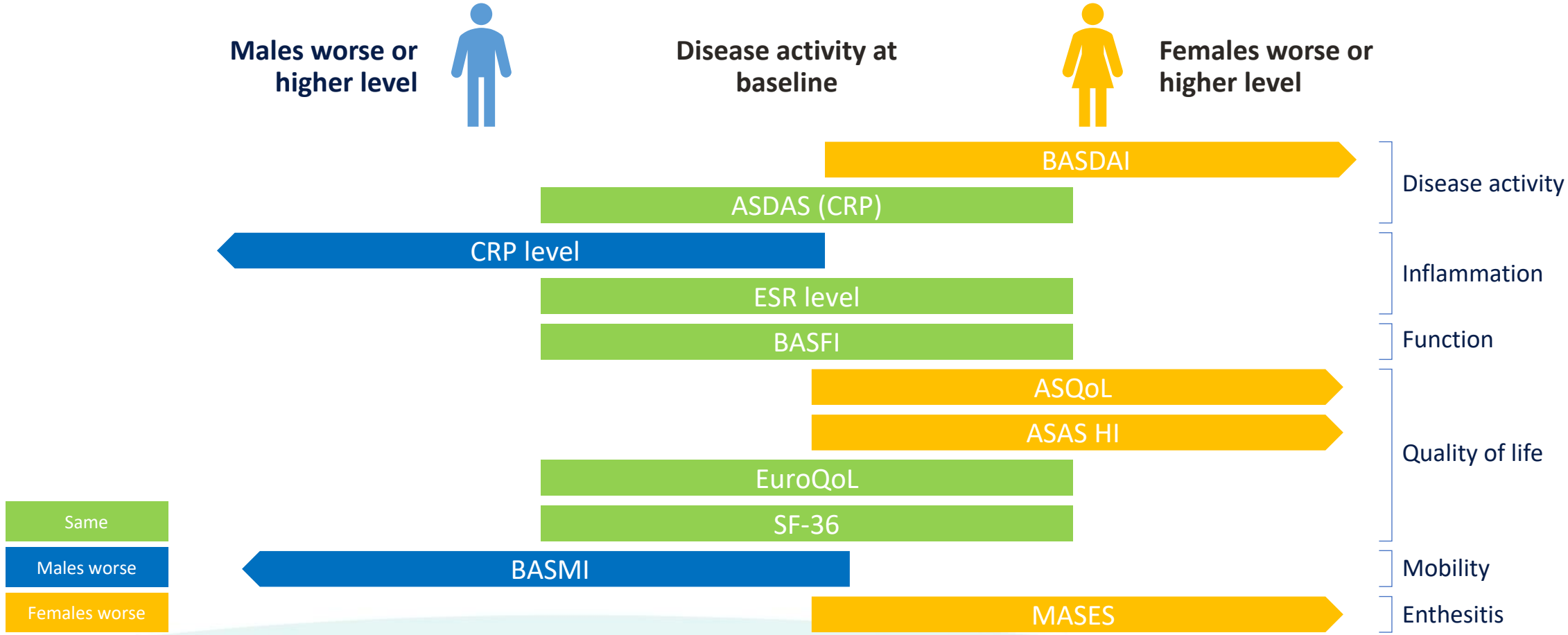
r-axSpA is **more prevalent** in males compared with females



*p<0.001 for r-axSpA vs nr-axSpA

axSpA, axial spondyloarthritis; nr-axSpA, non-radiographic axial spondyloarthritis; r-axSpA, radiographic axial spondyloarthritis

Males and females show differences in disease activity, function, and physical measures



Adapted from: Rusman T et al. Rheumatology 2020;59:iv38–iv48.

Gender effects in TNF-inhibitor treatment response

Study	AS or axSpA	Study design	Participants (male:female)	Treatment response (male vs female)	TNF-naive population	Follow-up period
Rusman et al., 2021	AS	Prospective cohort study	235:121	ASDAS: 64% vs 47% (RR 1.4, 95% CI 1.1–1.9)[a]	Yes	6 months
Sieper et al., 2019	nr-axSpA	Open-label prospective study	295:301	ASDAS partial remission: OR 2.4, 95% CI 1.6–3.6[a]	Yes	12 weeks
Hebeisen et al., 2018	AS	Prospective cohort study	294:146	ASAS20: OR 0.34, 95% CI 0.16–0.71[a]; ASDAS <1.3: OR 0.10, 95% CI 0.03–0.31[a] (inverse female/male)	Yes	1 year
van der Horst-Bruinsma et al., 2013	AS	Pooled data clinical controlled trials	957:326	ASDAS: 89.4% vs 68.4%[a]	Yes	12 weeks
Arends et al., 2011	AS	Prospective longitudinal observational cohort	152:68	ASAS20 and ASAS40: greater response in men than in women[a]	Yes	ASAS20: 3 months and 6 months; ASAS40: 6 months
Glintborg et al., 2010	AS	Observational cohort	364:239	Change in BASDAI: 27 vs 22	Yes	6 months

[a] prospective studies

Adapted from Stovall, R. *Nat Rev Rheumatol* **18**, 657–669 (2022)

Men shows greater adherence to anti TNF R/

Study	AS or axSpA	Study design	Participants (♂/♀)	Treatment adherence[a] (♂/♀)	Study time period
Hebeisen et al., 2018	AS	Prospective cohort study	294/146	**5.2** vs 2.9 years[b]	12 years
Al Arashi et al., 2018	AS	Prospective cohort	205/75	**91.6** vs 34.4 months[b]	Mean 6.3 years
Iannone et al., 2017	SpA	Prospective observational cohort	72/75	**23.0** vs 19.6 months[b]	2 years
Rusman et al., 2018	AS	Prospective cohort	74/48	**44.9** vs 33.4 months[b]	Mean 4.8 years
Flouri et al., 2018	AS	Prospective observational cohort	446/115	HR for R/ discontinuation in ♂/♀: **0.73** (95% CI 0.51–1.04)	10 years
Arends et al., 2011	AS	Prospective longitudinal observational cohort	152/68	HR for R/ discontinuation in ♂/♀: **0.41** (95% CI 0.25–0.66)[b]	6 months
Kristensen et al., 2010	AS	Prospective observational cohort	182/61	HR for R/ discontinuation in ♂/♀: **0.36** (95% CI 0.19–0.68)[b]	2 years
Glintborg et al., 2010	AS	Observational cohort	364/239	HR for R/ discontinuation in ♀/♂: **1.46** (95% CI 1.07–2.00)[b]	5 years
Yahya et al., 2018	axSpA	Retrospective review of routinely recorded clinical data	386/115	No gender effects observed	1, 5 and 10 years

Adapted from Stovall, R. *Nat Rev Rheumatol***18**, 657–669 (2022)

Estimated retention rate during the 1st year of secukinumab treatment according to diagnosis, gender, and BMI.

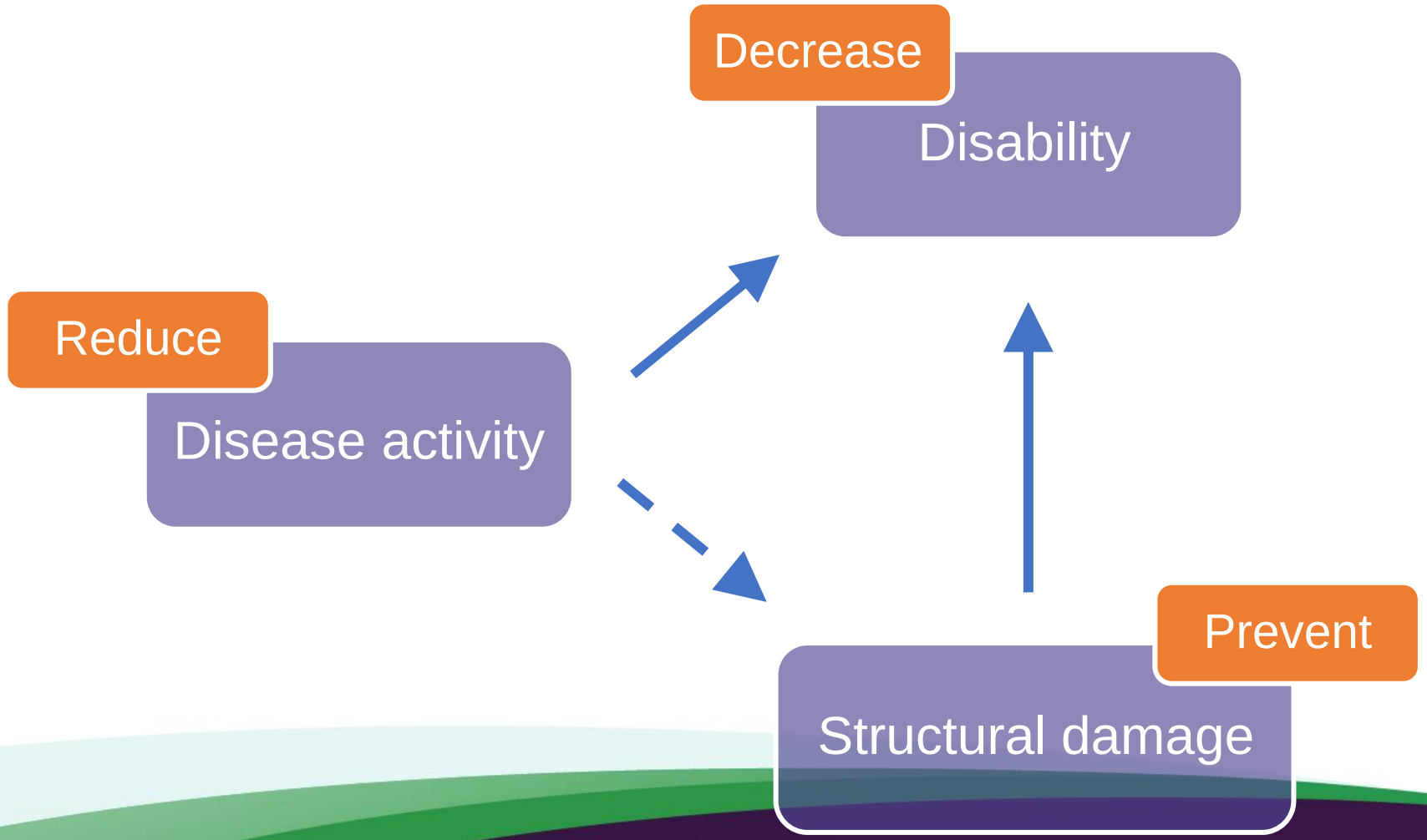
Diagnosis	Retention %	95%CI	Gender	Retention %	95%CI	BMI	Retention %	95% CI
AxSpA	82%	(74%; 89%)	Female	95%	(93%; 97%)	<30 kg/m^2	93%	(89%; 96%)
						≥30 kg/m^2	99%	(98%; 100%)
			Male	77%	(68%; 86%)	<30 kg/m^2	80%	(72%; 89%)
						≥30 kg/m^2	64%	(50%; 78%)
PsA	78%	(70%; 87%)	Female	66%	(54%; 79%)	<30 kg/m^2	57%	(42%; 73%)
						≥30 kg/m^2	91%	(87%; 95%)
			Male	89%	(84%; 93%)	<30 kg/m^2	91%	(88%; 96%)
						≥30 kg/m^2	81%	(73%; 89%)

Patients (*n* = 138) diagnosed with AxSpA by ASAS (*n* = 77) or PsA by CASPAR) (*n* = 61)

Garcia-Dorta A, Front Med 2022

Department of Rheumatology,University Hospitals Leuven
Skeletal Biology and Engineering Research Center (SBE), Dept Development and Regeneration, KULeuven

Treatment goals in chronic arthritis



Potential treat to target strategies in axial spondyloarthritis

Risk	Disease		Structural damage			Cardiovascular diseases			
Reversible Predisposing factor	Smoking	Smoking	Biological inflammation	Disease activity	Smoking	NSAID intake	Obesity	Hypertension	Diabetes
Outcome measure	Smoking status	Smoking Status	CRP*	ASDAS	Smoking Status	- dose and frequency	Body Mass index	Blood pressure	Hb A1C
Threshold (TARGET)	Cessation	Cessation	<ULN*	<1.3 or <2.1	Cessation	Cessation?	Normal range	<130mHg systolic <80 mHg diastolic	<7%
Time to Reach the target	<6 months	<6 months	<6 months	<6 months	<6 months	<6 months	<12 months	<3 months	<3 months

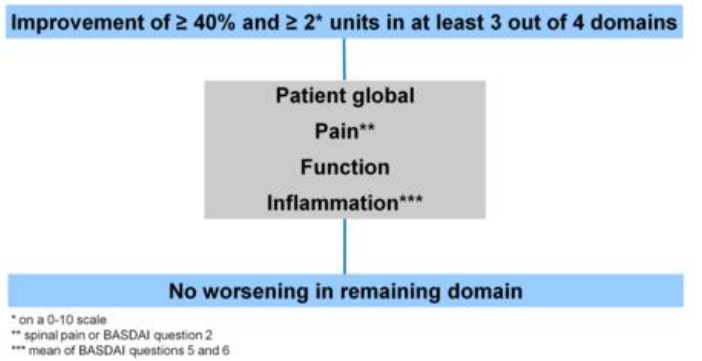
Dougados M, J Autoimm 2020

Department of Rheumatology,University Hospitals Leuven
Skeletal Biology and Engineering Research Center (SBE),Dept Development and Regeneration, KULeuven

What currently defines HCPs treatment & management of AxSpA (AS & nr-AxSpA)?

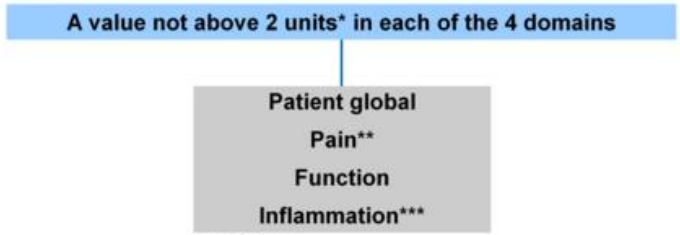
✓*Do you employ treat-to-target strategies in your practice? Which target do you aim for?*

ASAS 40 Improvement Criteria



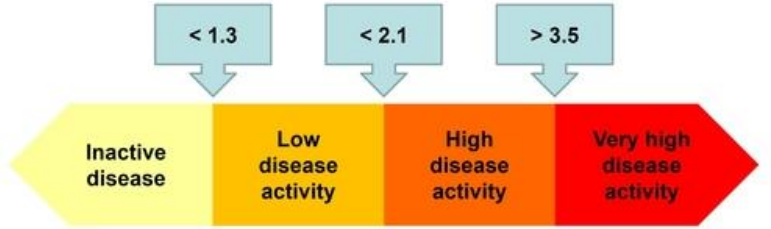
Adapted from Brandt J et al. Ann Rheum Dis 2004;63:1438-44 (with permission)

ASAS Partial Remission Criteria



Anderson JJ et al. Arthritis Rheum 2001;44:1876-86

ASDAS Cut-Offs for Disease Activity States

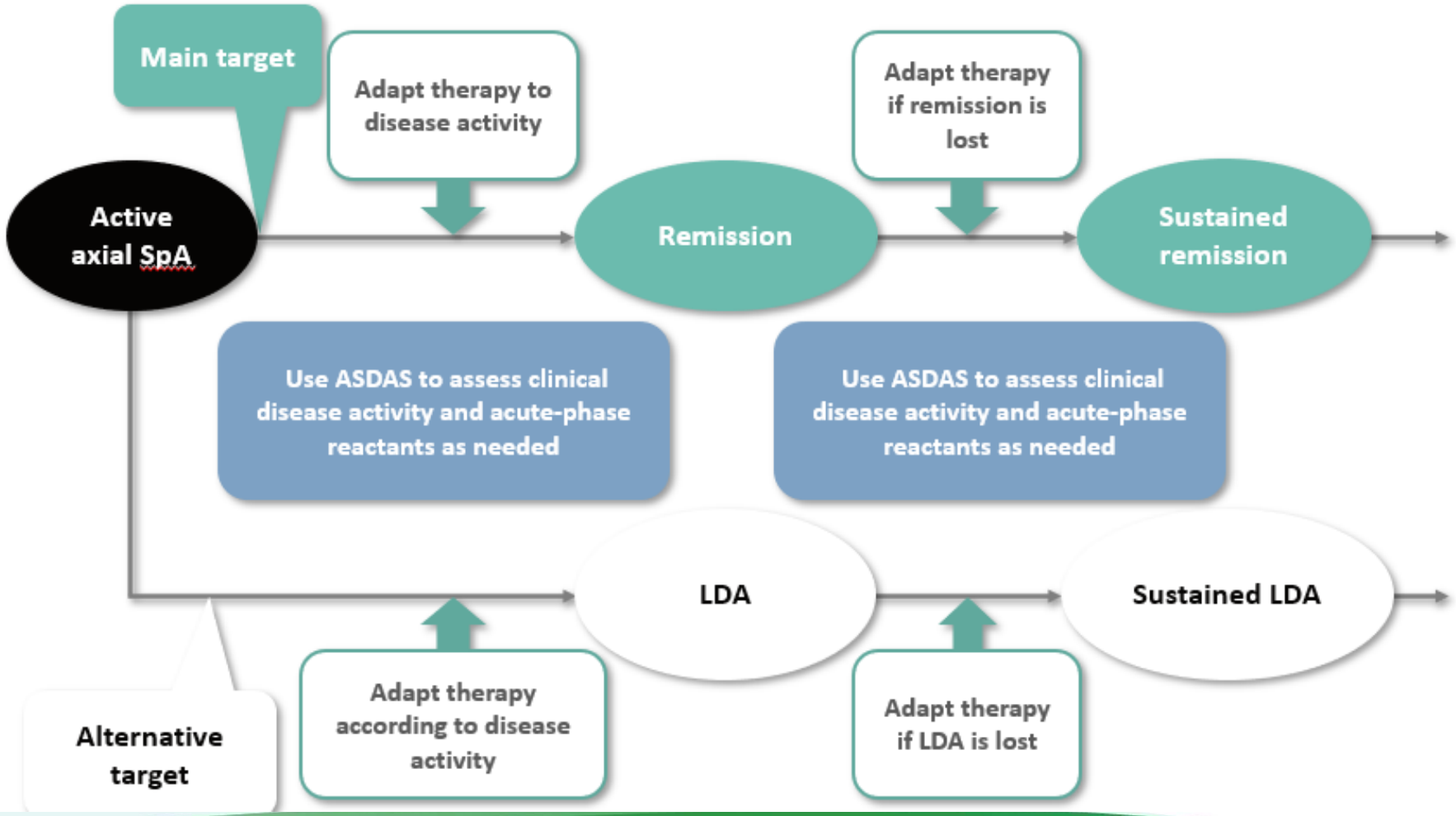


Machado P et al. Ann Rheum Dis 2011;70:47-53 (with permission)
Machado P et al. Ann Rheum Dis 2018;77:1539-40 (with permission)

- Spinal pain (back, neck, hips)
- Duration of morning stiffness
- Peripheral joint pain/swelling
- Patient global assessment of disease activity
- hs-CRP

axSpA, axial spondyloarthritis; AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial spondyloarthritis

Treat-to-target algorithm for axial spondyloarthritis

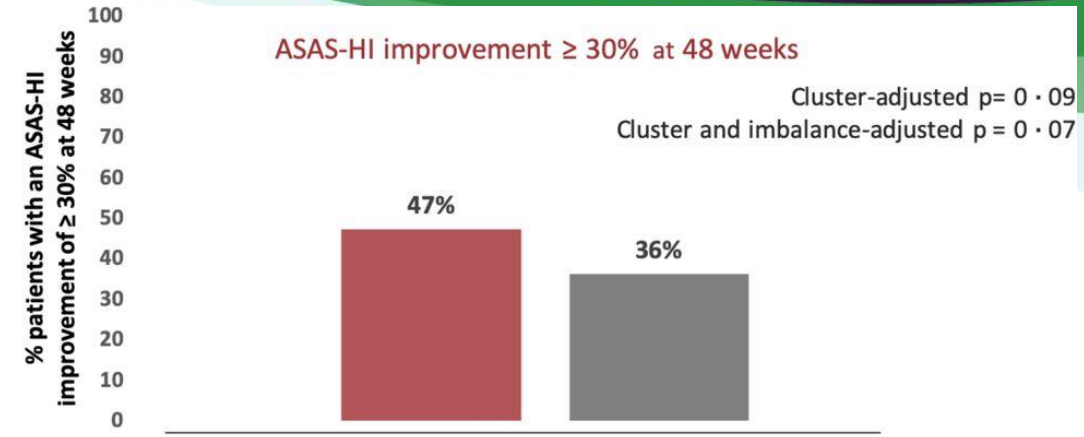


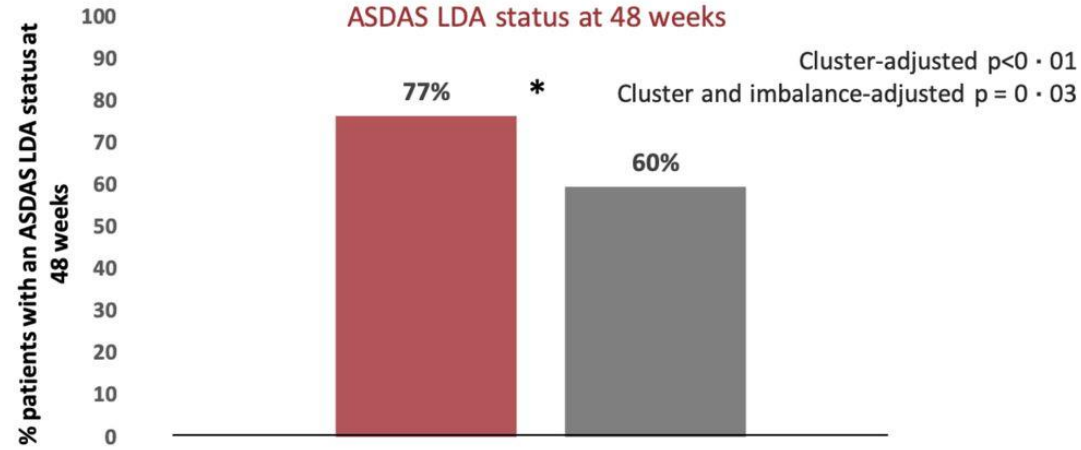
ASDAS, Ankylosing Spondylitis Disease Activity Score; LDA, low disease activity; SpA, spondyloarthritis

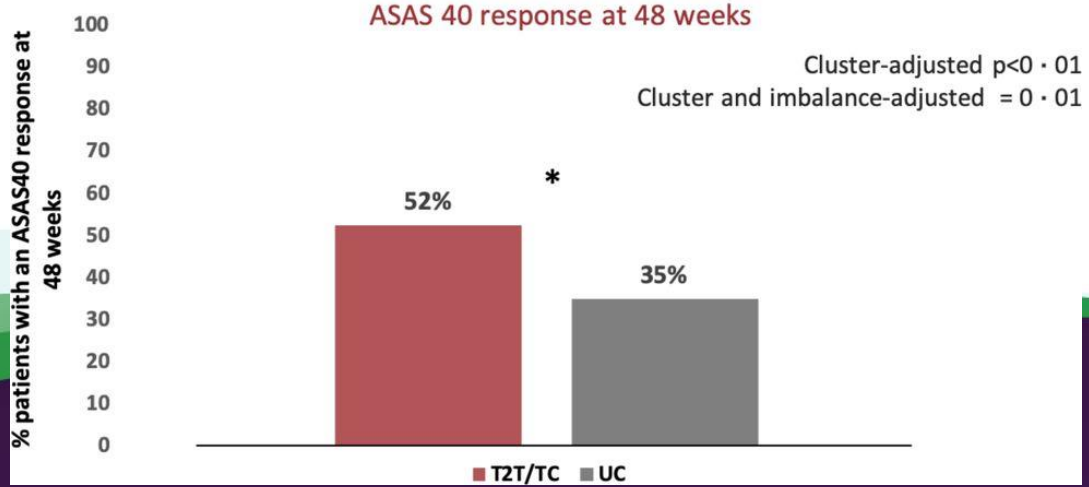
Smolen JS et al. Ann Rheum Dis 2018;77:3-17

TICOSPA:

ASAS-HI improvement ≥30%, ASDAS LDA status and ASAS40 response estimated at 48 weeks.





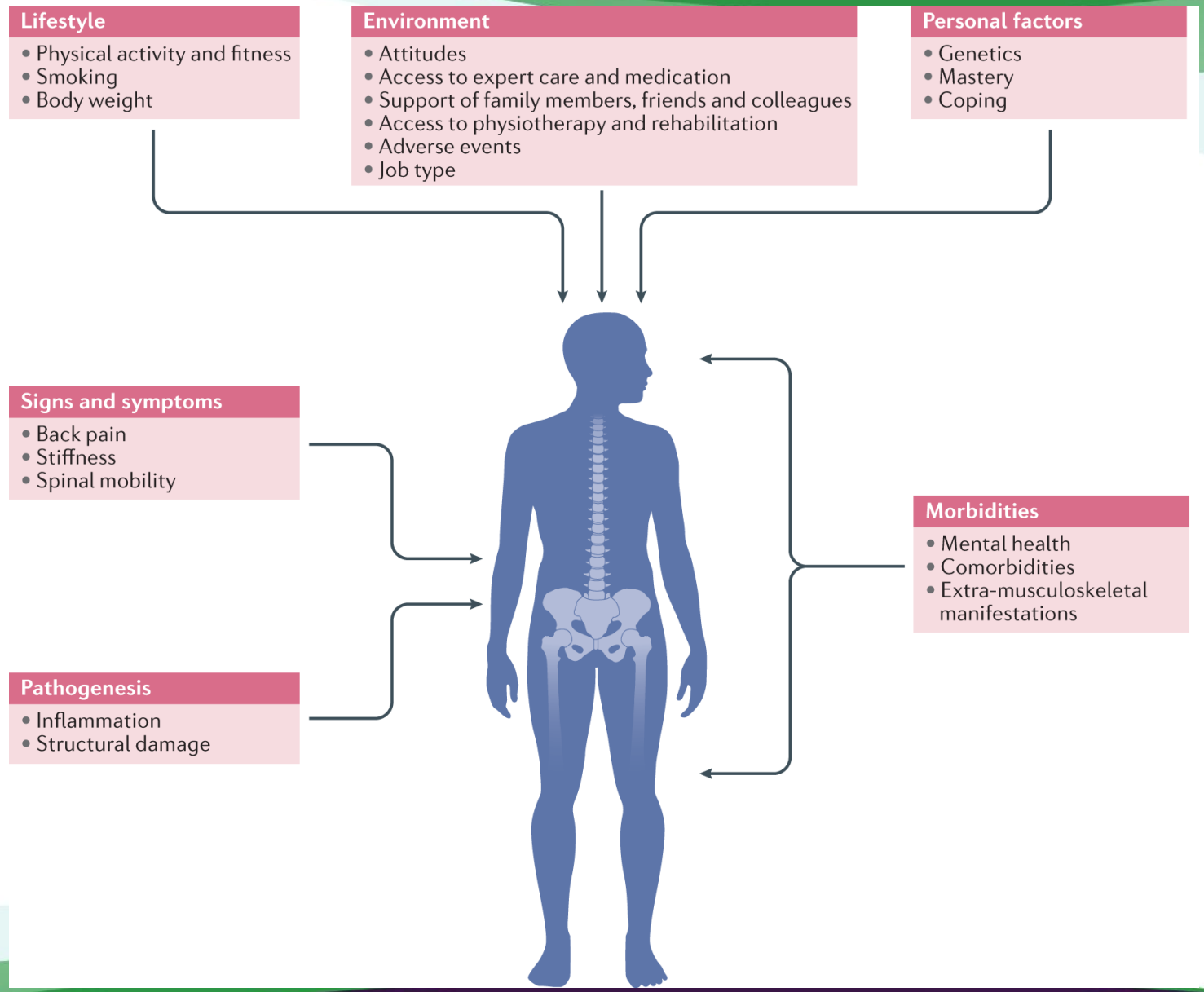


Anna Molto et al. Ann Rheum Dis 2021;80:1436-1444

GRAPPA
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

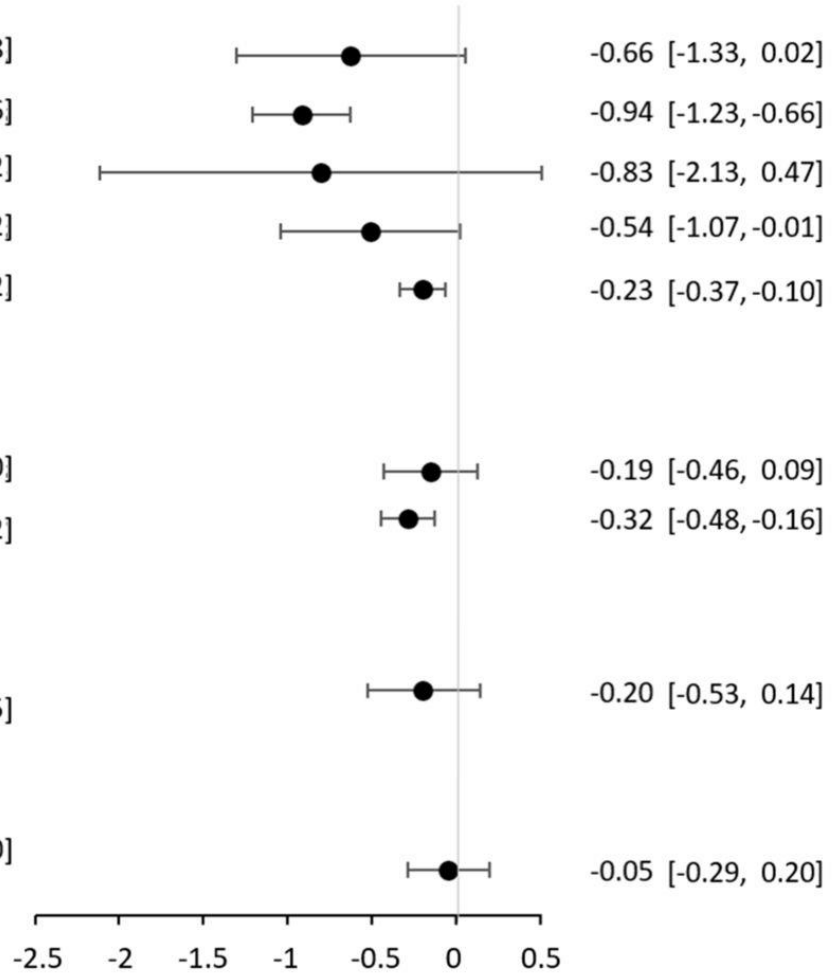
- Treat-to-target in axial spondyloarthritis — what about physical function and activity

Factors that affect physical function in axial spondyloarthritis.



Braun, J. *Nat Rev Rheumatol* **17**, 565–576 (2021)

Interventions	Included studies	SMD, 95% CI
Physical activity or exercise		
Systemic Sclerosis	[48, 78]	-0.66 [-1.33, 0.02]
Spondyloarthritis	[39, 47, 53, 64, 69, 71, 77, 106]	-0.94 [-1.23, -0.66]
Sjogren's Syndrome	[50, 62]	-0.83 [-2.13, 0.47]
Systemic Lupus Erythematosus	[44, 56, 60, 66, 72]	-0.54 [-1.07, -0.01]
Rheumatoid Arthritis	[40, 42, 45, 51, 52, 54, 57, 59, 60, 63, 75, 102]	-0.23 [-0.37, -0.10]
Psychoeducational interventions		
Systemic Lupus Erythematosus	[80, 86, 90]	-0.19 [-0.46, 0.09]
Rheumatoid Arthritis	[81, 83-85, 87-89, 91-97, 99-102]	-0.32 [-0.48, -0.16]
Physical Activity or Exercise + Psychoeducational		
Rheumatoid Arthritis	[104, 105]	-0.20 [-0.53, 0.14]
Follow-up model in consultations		
Rheumatoid Arthritis	[108, 110]	-0.05 [-0.29, 0.20]



Eduardo José Ferreira Santos et al. RMD Open 2023;9:e003350

GRAPPA
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

Difficult to treat?
Difficult to manage?

Difficult to treat RA patients are well defined, but can the concept apply beyond RA?

GRAPPA
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

EULAR definition of D2T RA

- Treatment according to EULAR guidelines and failure of ≥2 b/tsDMARDs (with different mechanisms of action), after failure of csDMARD
- Suggestive evidence of disease activity/progression, defined as ≥1 of;
  - At least MDA (DAS28-ESR>3.2 or CDAI >10)
  - Signs (including biology and imaging) and/or symptoms suggesting active disease (joint or otherwise)
  - Inability to reduce systemic steroid therapy (<7.5 mg/day prednisone equivalent)
  - Rapid radiographic progression
  - Controlled disease, but with persistent RA symptoms causing reduced quality of life
- Management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient

All 3 criteria must be present

Caveats for applying to axSpA

- Only 3 classes of Tx (in RA there are 5)
- Could be defined as ASDAS-CRP >1.3 or possibly BASDAI >4/10
- CRP within normal limits is frequent in axSpA
- MRI primarily used at diagnostic stage
- Can allow for consideration of extra-rheumatological manifestations (e.g., uveitis, PsO and IBD)
- Systemic corticosteroids not indicated in axSpA
- Could be adapted to "unable to reduce/discontinue NSAIDs"
- Not applicable to axSpA
- Could be applied to axSpA and might include persistent pain
- Applicable but subjective

NO

axSpA, axial spondyloarthritis; ASDAS-CRP, ankylosing spondylitis disease activity score- C-reactive protein; BASDAI, bath ankylosing spondylitis disease activity index; b/tsDMARDs, biologic/targeted synthetic DMARDs; CDAI, clinical disease activity index; CRP, C-reactive protein; csDMARD, conventional synthetic DMARD; DAS28-ESR, disease activity score assessing 28 joints using erythrocyte sedimentation rate; D2T, difficult to treat; DMARD, disease-modifying antirheumatic drug; EULAR, European Alliance of Associations for Rheumatology; IBD, inflammatory bowel disease; MDA, moderate disease activity; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; PsO, psoriasis; RA, rheumatoid arthritis

Adapted from:
Wendling D, et al. Joint Bone Spine. 2023;90:105511.

GRAPPA
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

Abbreviations: D2T-axSpA: difficult-to-treat axial spondyloarthritis.

Factors associated with D2T axial SpA

Characteristic	Bivariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Female sex	1.93 (1.75 to 2.14)	<0.001	**1.79 (1.61 to 1.99)**	**<0.001**
Peripheral symptoms	2.02 (1.84 to 2.23)	<0.001	**1.84 (1.67 to 2.04)**	**<0.001**
Psoriasis	1.61 (1.46 to 1.77)	<0.001	**1.33 (1.20 to 1.47)**	**<0.001**
Inflammatory bowel disease	1.05 (0.91 to 1.22)	0.50	–	–
Severe uveitis	1.43 (0.78 to 2.65)	0.24	–	–
Diabetes	1.14 (0.95 to 1.38)	0.17	–	–
Dyslipidaemia	1.13 (0.98 to 1.30)	0.11	–	–
Hypertension	1.24 (1.11 to 1.38)	<0.001	**1.20 (1.06 to 1.36)**	**<0.001**
Severe smoking	1.47 (1.22 to 1.78)	<0.001	–	–
Severe obesity	1.99 (1.52 to 2.59)	<0.001	–	–
Depression	2.19 (1.98 to 2.43)	<0.001	**2.09 (1.87 to 2.33)**	**<0.001**

Adapted from Fakih O, *RMD Open* 2023

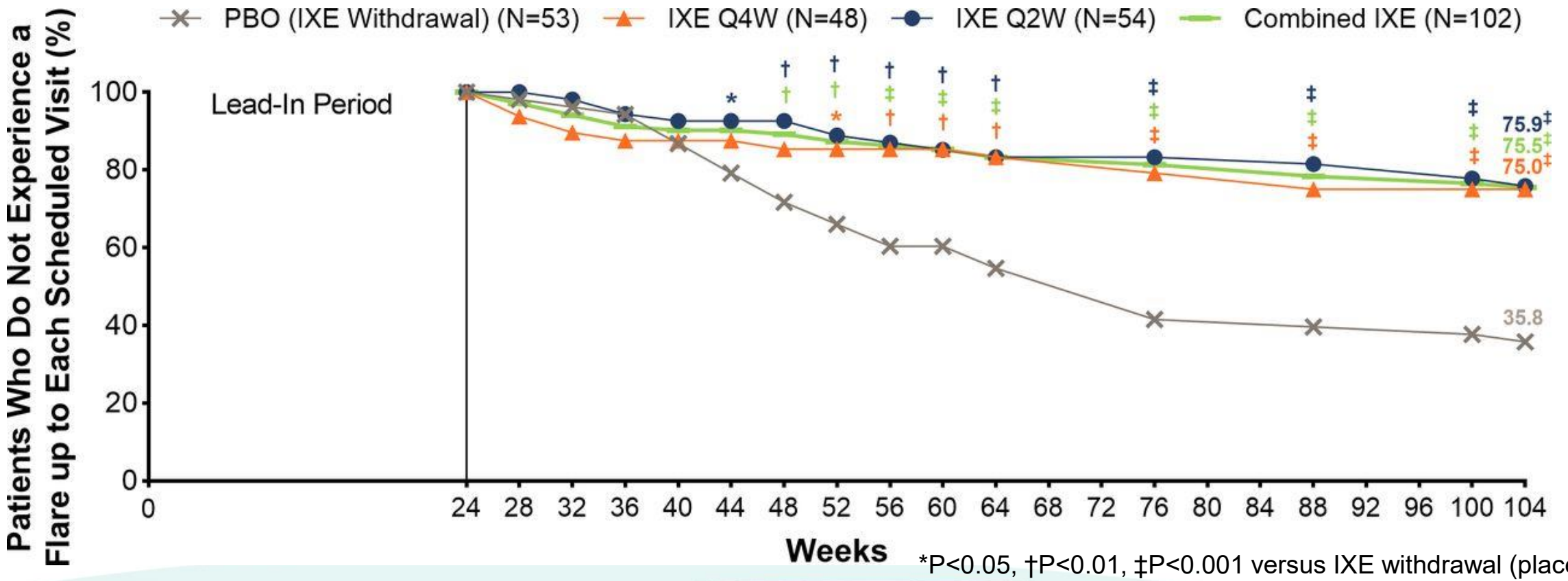
Approach to patients with axSpA, after multiple pharmacological therapy failures

- Is the diagnosis correct?
- Is the disease still active (consider C-reactive protein level, erythrocyte sedimentation rate, sacroiliac joint or spine MRI)
- What am I treating? Inflammation or structural damage?
- Is the patient compliant with treatment?
- Is fibromyalgia, depression or sleep disturbance causing the symptoms?
- Have I set realistic expectations with the patient (and myself)?
- Should I try sacroiliac joint corticosteroid injections, nerve ablation (pain clinic), intravenous pamidronate (a bisphosphonate), maximize NSAIDs, or conventional synthetic DMARDs?

Tapering – withdrawal in axSPA

Study	Study design; number of patients	Strategy	Results
ABILITY-3	Multi-centre, randomized, double-blind; 305	Adalimumab withdrawal. Patients who achieved inactive disease (ASDAS <1.3) with open-label adalimumab treatment were randomly assigned to treatment with adalimumab or placebo for 40 weeks	70% of patients continuing adalimumab did not experience flare, compared with **47% of those who received placebo**
RE-EMBARK	Multi-centre, open-label, phase IV trial; 119 (in the withdrawal phase)	Etanercept withdrawal. Patients who achieved inactive disease after treatment with etanercept (50 mg subcutaneously weekly) for 24 weeks discontinued treatment	**75% of patients experienced flare within 40 weeks;** 50% experienced flare within 16 weeks. The probability of experiencing ≥1 flare after etanercept withdrawal increased from 22% at week 4 to 67% at week 40
C-OPTIMISE	Two-part multi-centre phase IIIb, open-label; 313 randomized at week 48	CZP dose reduction or withdrawal study. Patients with ASDAS <1.3 after open-label treatment with CZP for 48 weeks[a] were randomized to CZP 200 mg subcutaneously every 2 weeks (CZPQ2W), CZP 200 mg subcutaneously every 4 weeks (CZPQ4W) or placebo for a further 48 weeks	83.7% of patients in the CZPQ2W group and 79.0% in the CZPQ4W group remained **flare free** through weeks 48–96, compared with **20.2% of patients in the placebo group**
COAST-Y	Double-blind RCT long-term extension; 155	IXE withdrawal Patients completing COAST-V, COAST-W and COAST-X trials (with ASDAS <1.3 at week 24[b]) were enrolled and treated with open label ixekizumab. Patients were randomized to IXE 80 mg Q4W, 80 mg Q2W or placebo for the next 40 weeks	83% of patients are flare free compared with **54% of those in the placebo group**

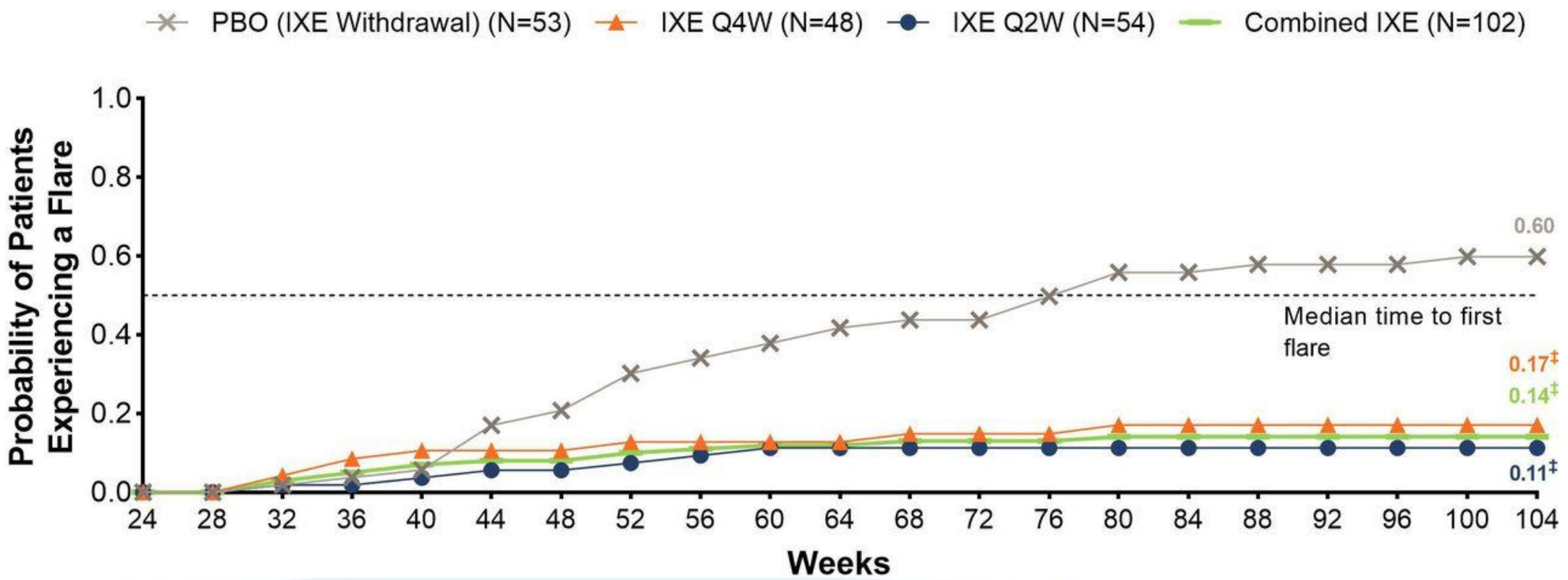
Proportion (%) of patients who remained flare-free through 104 weeks.



*P<0.05, †P<0.01, ‡P<0.001 versus IXE withdrawal (placebo).

Robert B M Landewé et al. Ann Rheum Dis 2023;82:212-216

estimate of time to first flare (weeks) through 104 weeks in placebo (IXE withdrawal) vs continuous IXE

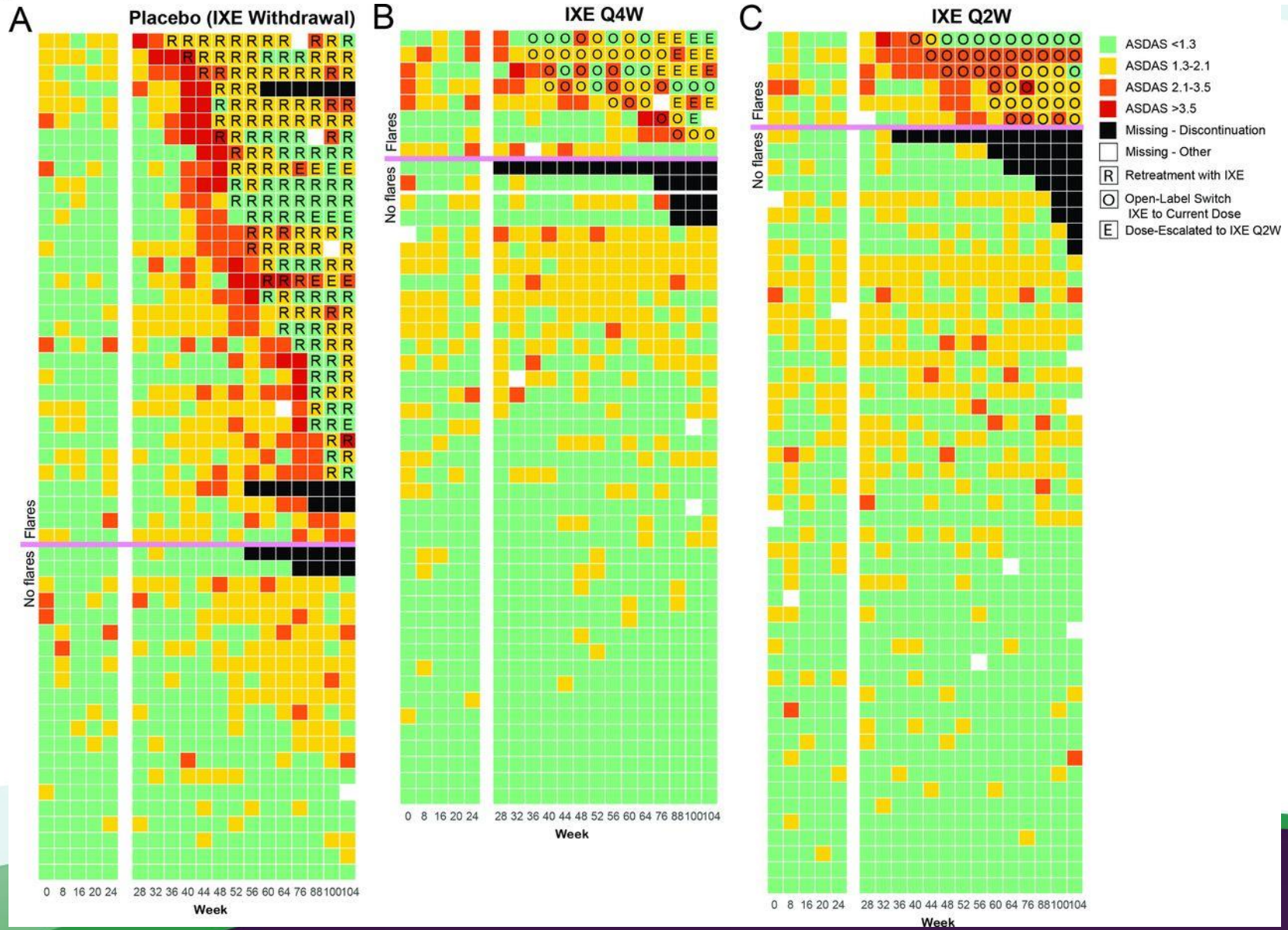


. ‡P<0.001 versus placebo (IXE withdrawal).

Robert B M Landewé et al. Ann Rheum Dis 2023;82:212-216

Sponsored by NOVARTIS

Heatmap diagram showing ASDAS disease activity status through 104 weeks



Robert B M Landewé et al. Ann Rheum Dis 2023;82:212-216

GRAPPA
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

Thank you for your attention !

GRAPPA
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

I am happy to take questions

GRAPPA
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

Department of Rheumatology, University Hospitals Leuven

Skeletal Biology and Engineering Research Center, Department of Development and Regeneration,
KU Leuven

Spondyloarthropathy Unit
K de Vlam
Rik Lories
Barbara Neerinckx
Alla Ishchenko
Pierrot Lebughe
Margot van Mechelen
Marlies Kaerts
Thijs Swinnen
Myroslawa Kulic

KATHOLIEKE UNIVERSITEIT LEUVEN

ored by OVARTIS