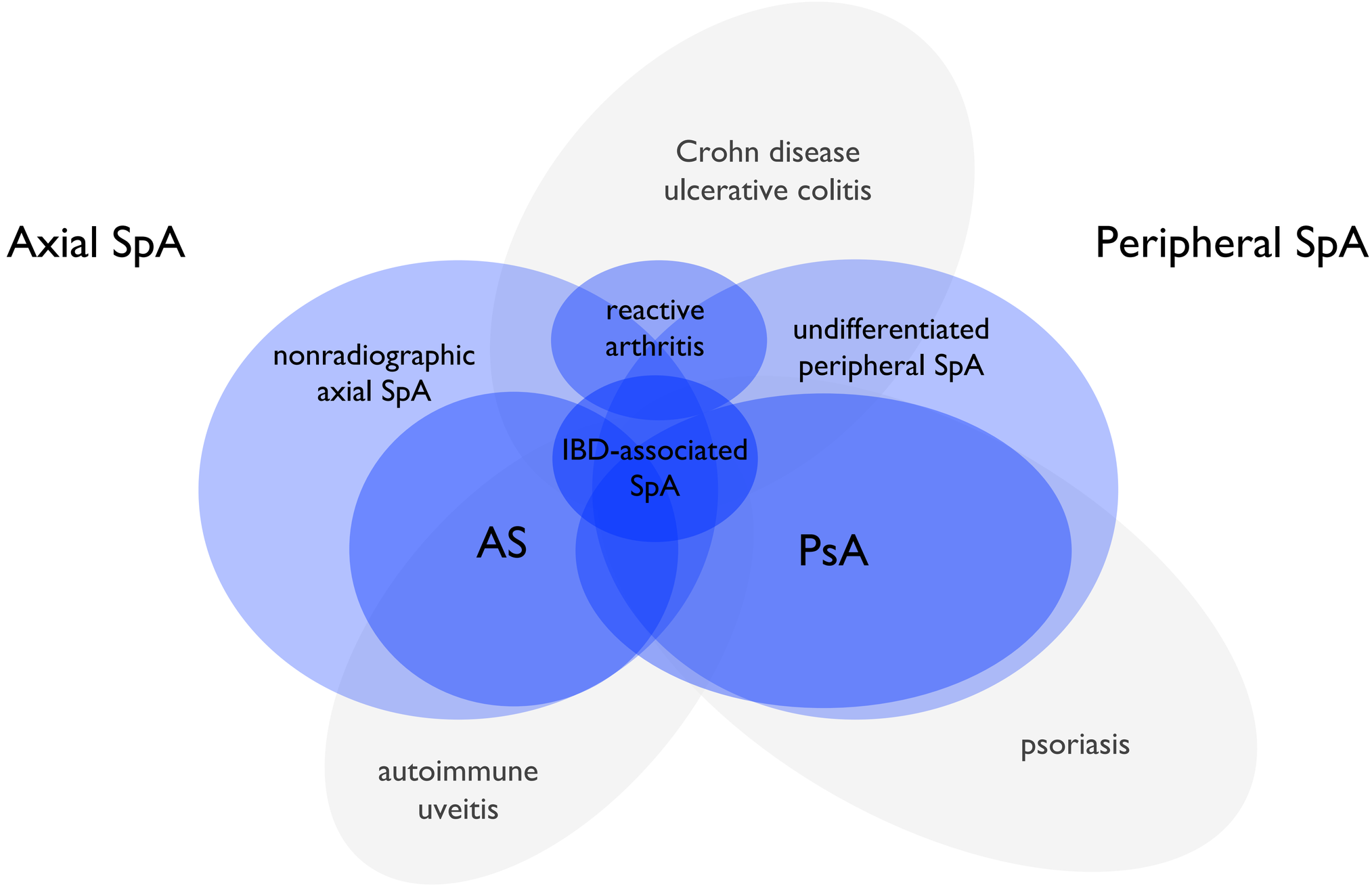
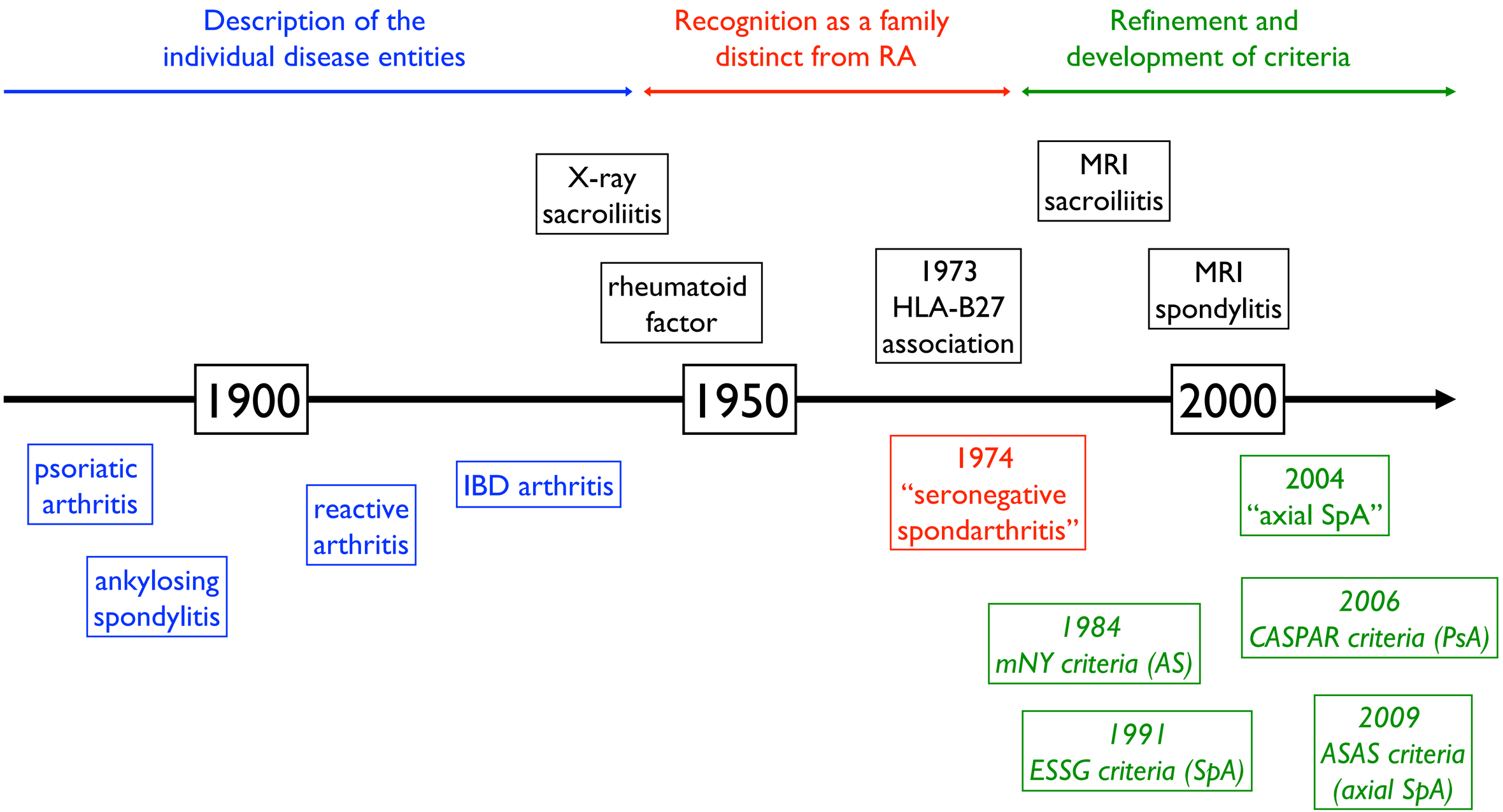
Managing Ankylosing Spondylitis in the Short- and Long-Term

Joerg Ermann, MD
Brigham and Women's Hospital
Harvard Medical School

Disclosures

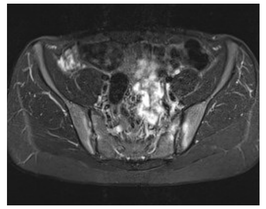
- Scientific Advisory Boards:
  Eli Lilly, Novartis, Pfizer, UCB
- Research Grants:
  Abbvie, Boehringer Ingelheim, Novartis, Pfizer


Axial SpA
Peripheral SpA
Crohn disease
ulcerative colitis
nonradiographic
axial SpA
reactive
arthritis
undifferentiated
peripheral SpA
IBD-associated
SpA
AS
PsA
autoimmune
uveitis
psoriasis


Description of the individual disease entities
Recognition as a family distinct from RA
Refinement and development of criteria
X-ray sacroiliitis
MRI sacroiliitis
rheumatoid factor
1973 HLA-B27 association
MRI spondylitis
1900
1950
2000
psoriatic arthritis
ankylosing spondylitis
reactive arthritis
IBD arthritis
1974 "seronegative spondarthritis"
2004 "axial SpA"
1984 mNY criteria (AS)
2006 CASPAR criteria (PsA)
1991 ESSG criteria (SpA)
2009 ASAS criteria (axial SpA)

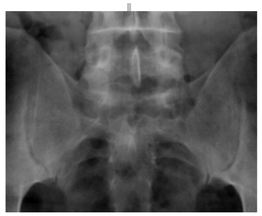
axial SpA

non-radiographic | radiographic (AS)



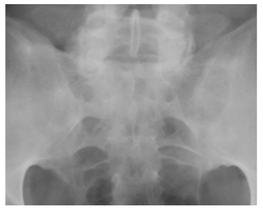
inflammatory back pain
other clinical SpA features

MRI sacroiliitis



inflammatory back pain
reduced spinal mobility

X-ray sacroiliitis
syndesmophytes



time [years]

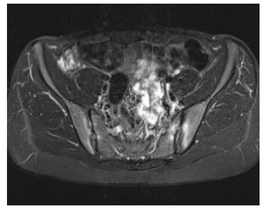
mNY criteria 1984

ASAS axial SpA criteria 2009

van der Linden Arthritis Rheum 1984; 27:361-8, Rudwaleit Ann Rheum Dis 2009; 68:777-83

axial SpA

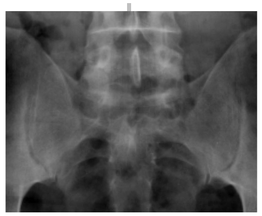
non-radiographic



inflammatory back pain
other clinical SpA features

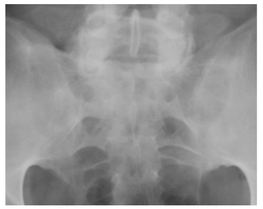
MRI sacroiliitis

radiographic (AS)



inflammatory back pain
reduced spinal mobility

X-ray sacroiliitis
syndesmophytes



time [years]

mNY criteria 1984

ASAS axial SpA criteria 2009

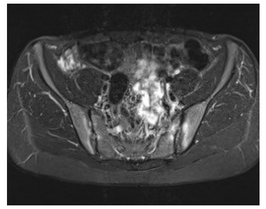
M:F = 1:1
HLA-B27 60%
less functional impairment

M:F = 2-3:1
HLA-B27 80-90%
longer disease duration

van der Linden Arthritis Rheum 1984; 27:361-8, Rudwaleit Ann Rheum Dis 2009; 68:777-83

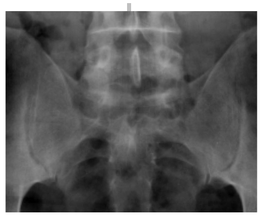
axial SpA

non-radiographic — radiographic (AS)



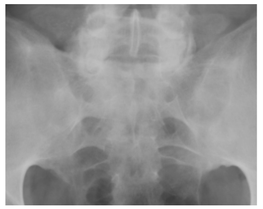
inflammatory back pain
other clinical SpA features

MRI sacroiliitis



inflammatory back pain
reduced spinal mobility

X-ray sacroiliitis
syndesmophytes



time [years]

mNY criteria 1984

ASAS axial SpA criteria 2009

non-radiographic axial SpA is a
"sub-optimal" category for clinical practice

van der Linden Arthritis Rheum 1984; 27:361-8, Rudwaleit Ann Rheum Dis 2009; 68:777-83

FDA vs. EMA drug label - what's the impact?

FDA

----------INDICATIONS AND USAGE----------

CIMZIA is a tumor necrosis factor (TNF) blocker indicated for:

- Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy (1.1)
- Treatment of adults with moderately to severely active rheumatoid arthritis (1.2)
- Treatment of adult patients with active psoriatic arthritis. (1.3)
- Treatment of adults with active ankylosing spondylitis (1.4)
- Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation (1.5)
- Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (1.6)

EMA

Axial spondyloarthritis

Cimzia is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising:

Ankylosing spondylitis (AS) (also known as radiographic axial spondyloarthritis)

Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Axial spondyloarthritis without radiographic evidence of AS (also known as non-radiographic axial spondyloarthritis)

Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated C-reactive protein (CRP) and /or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs.

The future of diagnostic coding: axSpA

ICD9-CM (1979)	
ankylosing spondylitis	720
spinal enthesopathy	720.1
sacroiliitis, not elsewhere classified	720.2
other inflammatory spondyloathy	720.89
unspecified inflammatory spondylopathy	720.9

ICD10-CM (2016)	
ankylosing spondylitis	M45.0 - M45.9
spinal enthesopathy	M46.0
sacroiliitis, not elsewhere classified	M46.1
non-radiographic axial spondyloarthritis (10/20)	M46.8
unspecified inflammatory spondylopathy	M46.9

ICD11	
axial spondyloarthritis	FA92.0
inflammatory spondyloarthritis spinal enthesitis	FA92.00
sacroiliitis, not elsewhere classified	F92.01
other specified axial spondyloarthritis	FA92.0Y
axial spondyloarthritis, unspecified (incl AS)	FA92.0Z

2009 ASAS classification criteria for axial SpA

(in patients with back pain ≧3 months and age at onset <45 years)

Sacroiliitis on imaging plus ≧1 SpA feature	or	HLA-B27 plus ≧2 other SpA features
Sacroiliitis on imaging • active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA OR • definite radiographic sacroiliitis according to mNY criteria *sensitivity 82.9%, specificity 84.4% (overall)* *sensitivity 66.2%, specificity 97.3% (imaging arm)*		• inflammatory back pain • arthritis • enthesis (heel) • uveitis • dactylitis • psoriasis • Crohn's disease/ulcerative colitis • good response to NSAIDs • family history for SpA • HLA-B27 • elevated CRP

Rudwaleit Ann Rheum Dis 2009; 68:777-83

Diagnosing axial SpA: not a simple YES or NO

	Diagnostic approach	Classification approach
Aim	To establish the diagnosis of a disease in clinical practice	To define a homogeneous group of patients for research purposes
The starting point	Suspicion of a disease with a certain level of a pre-test probability	Established diagnosis of a disease
Differential diagnoses or other conditions that might explain symptoms	Always considered	Not considered
Values of the positive diagnostic tests	Different and depend on the test itself, earlier screening or diagnostic tests performed, geographic region and background population	Few levels with the same value of parameters on the same level
Values of the negative diagnostic tests	Negative test results are considered; their diagnostic values depend on the same factors as for positive test results	Not considered except the situation that there are not enough positive test results to fulfil the criteria
Outcome	Probability of the disease presence	Yes or no answer (classification criteria fulfilled or not fulfilled) with a certain level of sensitivity and specificity
External reference ('gold standard')	None	Expert opinion derived during classification criteria development

Poddubbnyy Rheumatology 2021

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Vol. 0, No. 0, Month 2019, pp 1–15
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AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

SPECIAL ARTICLE

2019 Update of the American College of Rheumatology/ Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis

Michael M. Ward,[1] Atul Deodhar,[2] Lianne S. Gensler,[3] Maureen Dubreuil,[4] David Yu,[5] Muhammad Asim Khan,[6] Nigil Haroon,[7] David Borenstein,[8] Runsheng Wang,[9] Ann Biehl,[1] Meika A. Fang,[10] Grant Louie,[11] Vikas Majithia,[12] Bernard Ng,[13] Rosemary Bigham,[14] Michael Pianin,[15] Amit Aakash Shah,[16] Nancy Sullivan,[17] Marat Turgunbaev,[16] Jeff Oristaglio,[17] Amy Turner,[16] Walter P. Maksymowych,[18] and Liron Caplan[19]

update on 2016 recommendations, 86 recommendations
ACR-endorsed GRADE methodology for guideline development

Treatment of axSpA/AS - the basics

- No difference between nr-axSpA and AS
- NSAIDs are first-line drugs
  - no preference for specific NSAID
  - continuous preferred over on demand in active disease
  - advance therapy if insufficient response to ≧2 NSAIDs at full dose over 1 month (or intolerance)
- Physical therapy
- no role for conventional DMARDs,
  no systemic corticosteroids, but consider local injections

Treatment of axSpA/AS - the basics

- TNF and IL-17A inhibitors
  - current recommendations favor TNFi as first biologic
  - similar efficacy in clinical trials, no head-to-head studies
- Consider extra spinal disease manifestations
  - IBD: anti-TNF antibody
  - frequent, severe uveitis: anti-TNF antibody
  - severe psoriasis: IL-17A inhibitor
- Common IL-17A inhibitor adverse events: URTI, mucocutaneous candidiasis
- Monitor disease activity (ASDAI, ASDAS, RAPID3, CRP/ESR)
  - assess response 3 months after initiation/change of biologic
  - switch NSAID to on-demand if good response
  - primary vs. secondary biologic failure

BASDAI = Bath AS Disease Activity Index

1. How would you describe the overall level of fatigue/tiredness you have experienced? fatigue
2. How would you describe the overall level of AS neck, back or hip pain you have had? back pain
3. How would you describe the overall level of pain/swelling in joints other than neck, back, hips you have had? peripheral arthritis
4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure? enthesitis
5. How would you describe the overall level of morning stiffness you have had from the time you wake up? severity of morning stiffness
6. How long does your morning stiffness last from the time you wake up? (0-2 hours) duration of morning stiffness

6 questions (visual analog or numerical rating scale)
range 0-10
BASDAI ≧4 indicates active disease

$$\text{BASDAI} = \frac{Q1 + Q2 + Q3 + Q4 + \left(\frac{Q5 + Q6}{2}\right)}{5}$$

Garrett J Rheumatol 1994; 21:2286-91

ASDAS = AS Disease Activity Score

- Parameters
  - back pain [0-10] (BASDAI Q2)
  - duration of morning stiffness [0-10] (BASDAI Q6)
  - patient global assessment [0-10]
  - peripheral joint pain/swelling [0-10] (BASDAI Q3)
  - CRP [mg/l] or ESR [mm/h]
- ASDAS-CRP
  0.12 x back pain + 0.06 x duration of morning stiffness + 0.11 x patient global
  + 0.07 x peripheral joint pain/swelling + 0.58 x Ln(CRP+1)
  (if CRP < 2 mg/l → use 2 for calculation)

- Current disease activity
  inactive, low ≧1.3, high ≧2.1, very high ≧3.5
- Change in disease activity
  clinically important ≧1.1
  major improvement ≧2.0

Lukas Ann Rheum Dis 2009; 68:18-24, Machado Ann Rheum Dis 2011; 70:47-53, Machado Arthritis Rheum 2015; 67:408-13

RAPID3 correlates strongly with BASDAI and ASDAS

RAPID3

(Routine Assessment of Patient Index Data 3)

1. Please check (✓) the **ONE** best answer for your abilities at this time:

OVER THE PAST WEEK, were you able to:	Without **ANY** difficulty	With **SOME** difficulty	With **MUCH** difficulty	**UNABLE** to do
Dress yourself, including tying shoelaces and doing buttons?	☐ 0	☐ 1	☐ 2	☐ 3
Get in and out of bed?	☐ 0	☐ 1	☐ 2	☐ 3
Lift a full cup or glass to your mouth?	☐ 0	☐ 1	☐ 2	☐ 3
Walk outdoors on flat ground?	☐ 0	☐ 1	☐ 2	☐ 3
Wash and dry your entire body?	☐ 0	☐ 1	☐ 2	☐ 3
Bend down to pick up clothing from the floor?	☐ 0	☐ 1	☐ 2	☐ 3
Turn regular faucets on and off?	☐ 0	☐ 1	☐ 2	☐ 3
Get in and out of a car, bus, train, or airplane?	☐ 0	☐ 1	☐ 2	☐ 3
Walk two miles?	☐ 0	☐ 1	☐ 2	☐ 3
Participate in sports and games as you would like?	☐ 0	☐ 1	☐ 2	☐ 3

2. How much pain have you had because of your condition OVER THE PAST WEEK? Please indicate below how severe your pain has been:

NO PAIN ○○○○○○○○○○○○○○○○○○○○ PAIN AS BAD AS IT COULD BE

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

3. Considering all the ways in which illness and health conditions may affect you at this time, please indicate below how you are doing:

VERY WELL ○○○○○○○○○○○○○○○○○○○○ VERY POORLY

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6 6.5 7 7.5 8 8.5 9 9.5 10

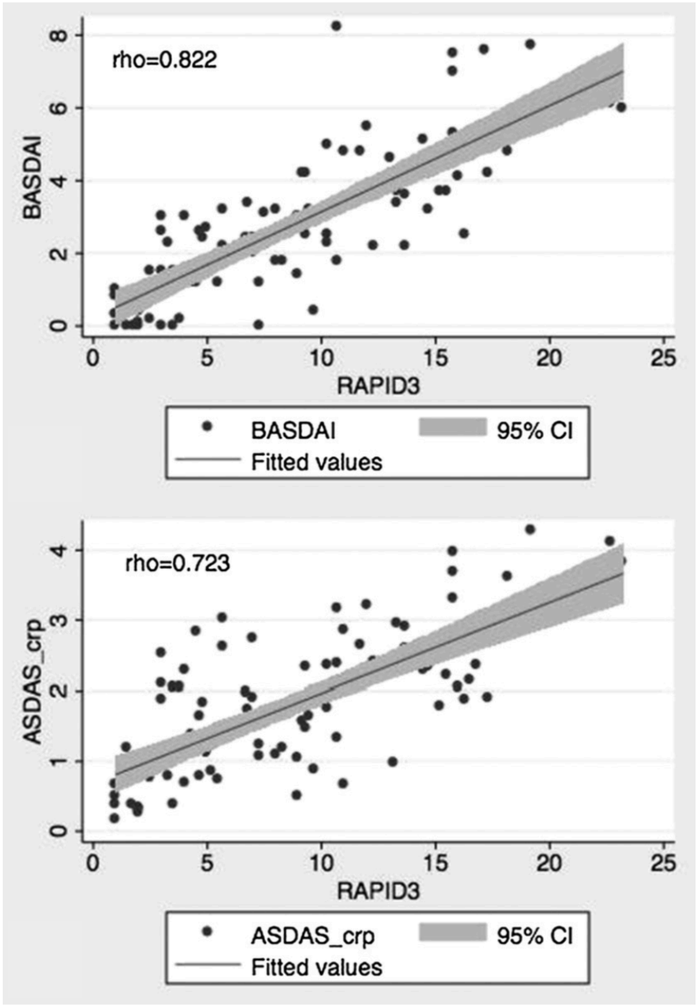
FN ☐

1=0.3 16=5.3
2=0.7 17=5.7
3=1.0 18=6.0
4=1.3 19=6.3
5=1.7 20=6.7
6=2.0 21=7.0
7=2.3 22=7.3
8=2.7 23=7.7
9=3.0 24=8.0
10=3.3 25=8.3
11=3.7 26=8.7
12=4.0 27=9.0
13=4.3 28=9.3
14=4.7 29=9.7
15=5.0 30=10

PN ☐

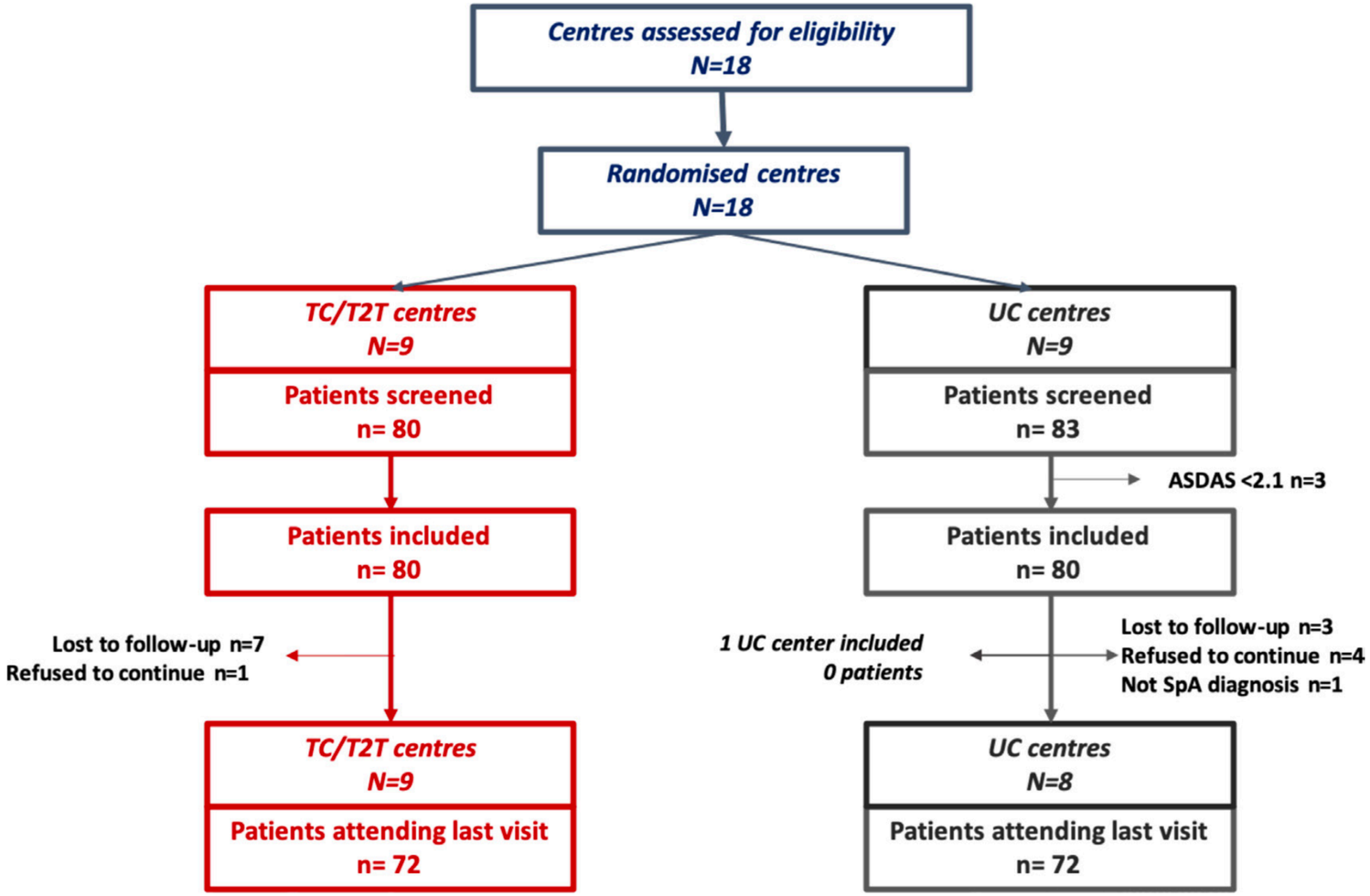
PTGL ☐

RAPID ☐ (0-30)



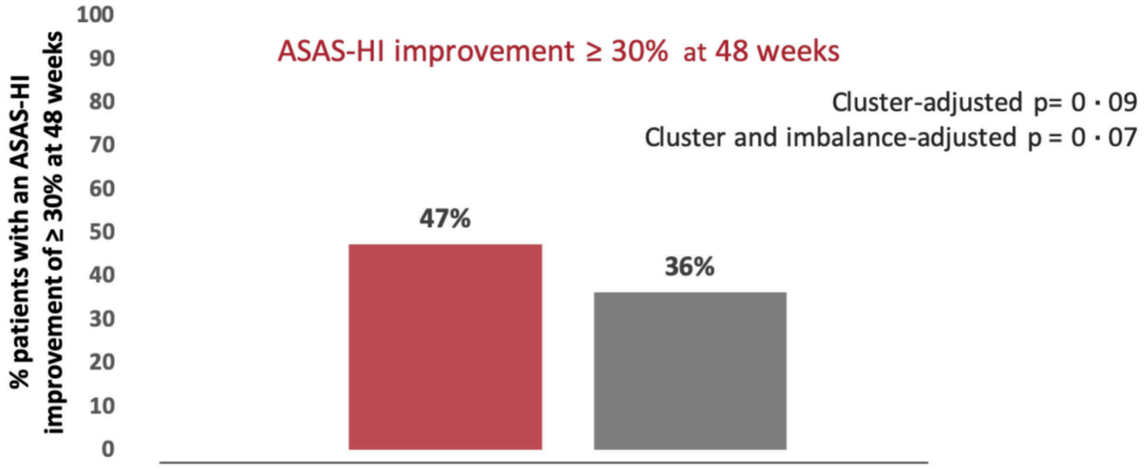
Park J Clin Rheumatol 2015; 21:300-4, Cinar Rheumatol Int 2015; 35:1575-80, Castrejon RMD Open 2016; 2:e000235

Is treat-to-target a viable strategy in axSpA/AS?
Results from TICOSPA = Tight Control in Spondyloarthritis



Molto Ann Rheum Dis 2021

TICOSPA failed its primary endpoint



Primary endpoint
ASAS -HI at 48 weeks

- Statistical significance in secondary endpoints, e.g.
  ASAS40 response 52% vs. 35%, p=0.01
- Study design issues:
  usual care too good?
  (academic medical centers)
- AScalate - ongoing T2T study

Molto Ann Rheum Dis 2021

Treatment of axSpA/AS - FAQs

1. Am I going to be crippled?
2. What is the impact of the disease on a future pregnancy?
3. Do I have to inject these medication for the rest of my life?
4. Is there anything else I can do? What about diet?
5. What if this medication stops working?

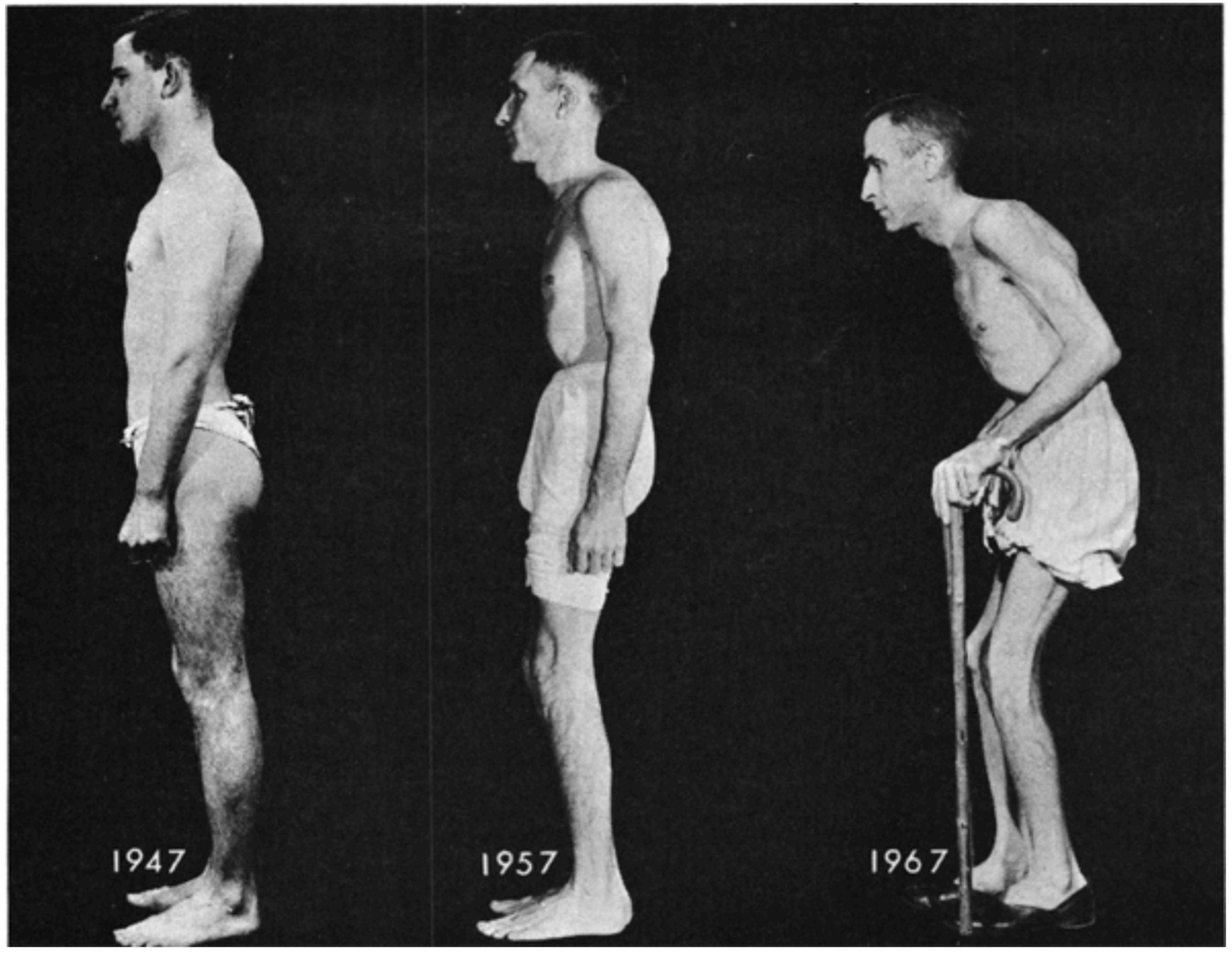


Figure 1. ***Ankylosing spondylitis. In 1947, at the age of 22 years, the patient had a normal posture. By 1957 there was forward protrusion of the neck with high dorsal kyphosis and a flat lumbar segment. By 1967 there was accentuation of the deformity due to flexion contracture at the hips.***

Ogryzlo Postgrad Med 1969; 45:182-8

Disease course in axSpA/AS is highly variable

Table 1. Rates and predictors of progression to radiographic axial spondyloarthritis in spondyloarthritis patients without initial structural damage in the sacroiliac joints – summary of published data.

Study	No. of SpA (nr-axSpA) patients	Initial diagnosis/classification	Follow-up duration	Progression rate to AS/r-axSPA	Factors associated with progression
Sany et al. [29]	23 (23)	Seronegative HLA-B27-associated inflammatory rheumatic disease	28 months	30%	–
Schattenkirchner et al. [30]	119 (119)	HLA-B27-positive oligoarthritis	2–6 years + 6 years	25.2% + 4.2%	–
Mau et al. [26]	88 (88)	'Possible' AS	10 years	36%	HLA-B27 positivity
Oostveen et al. [28]	25 (23)	HLA-B27 positivity and ILBP	3 years	43.5%	Structural changes on MRI
Kumar et al. [21]	35 (35)	SpA (ESSG criteria)	11 years	42.9%	–
Sampaio-Barros et al. [22]	68 (68)	SpA (ESSG criteria)	2 years	10%	Buttock pain
Huerta-Sil et al. [23]	62 (62)	SpA (ESSG criteria)	3.3 years	34%	Low-grade sacroiliitis, history of uveitis
Bennett et al. [24]	50 (42)	SpA (ESSG criteria)	8 years	12%	Severe sacroiliitis on MRI, HLA-B27 positivity
Sampaio-Barros et al. [25]	111 (111)	SpA (ESSG criteria)	10 years	24.3%	Buttock pain, HLA-B27 positivity
Poddubnyy et al. [15]	210 (95)	Nr-axSpA (modification of the ESSG criteria)	2 years	3.8%*	Elevated CRP at baseline
Aydin, et al. [14]	29 (21)	Nr-axSpA (ASAS criteria)	7.7 years	14.3%	Active sacroiliitis on MRI
Backland et al. [13]	28 (20)	Nr-axSpA (ASAS criteria)	8 years	20%	–
Ruderman et al. [17]	286 (120)	Nr-axSpA (ASAS criteria)	11 years	10%	–
Wang et al. [16]	83 (83)	Nr-axSpA (ASAS criteria)	10 years	19%	Fulfillment of the imaging arm of the ASAS axSpA criteria
Dougados et al. [19]	449 (326)	Nr-axSpA (ASAS criteria)	2 years	2.0%*	Smoking, HLA-B27 positivity, active sacroiliitis on MRI
Sepriano et al. [20]	357 (295)	Nr-axSpA (ASAS criteria)	4.4 years	5%*	–
Dougados et al. [18]	416 (354)	Nr-axSpA (ASAS criteria)	5 years	5.1%*	Elevated CRP, HLA-B27 positivity, active sacroiliitis on MRI
Constantino et al. [34]	953 (446)	Nr-axSpA (ASAS criteria)	8.3 years	8.1%	Low-grade sacroiliitis, axial disease

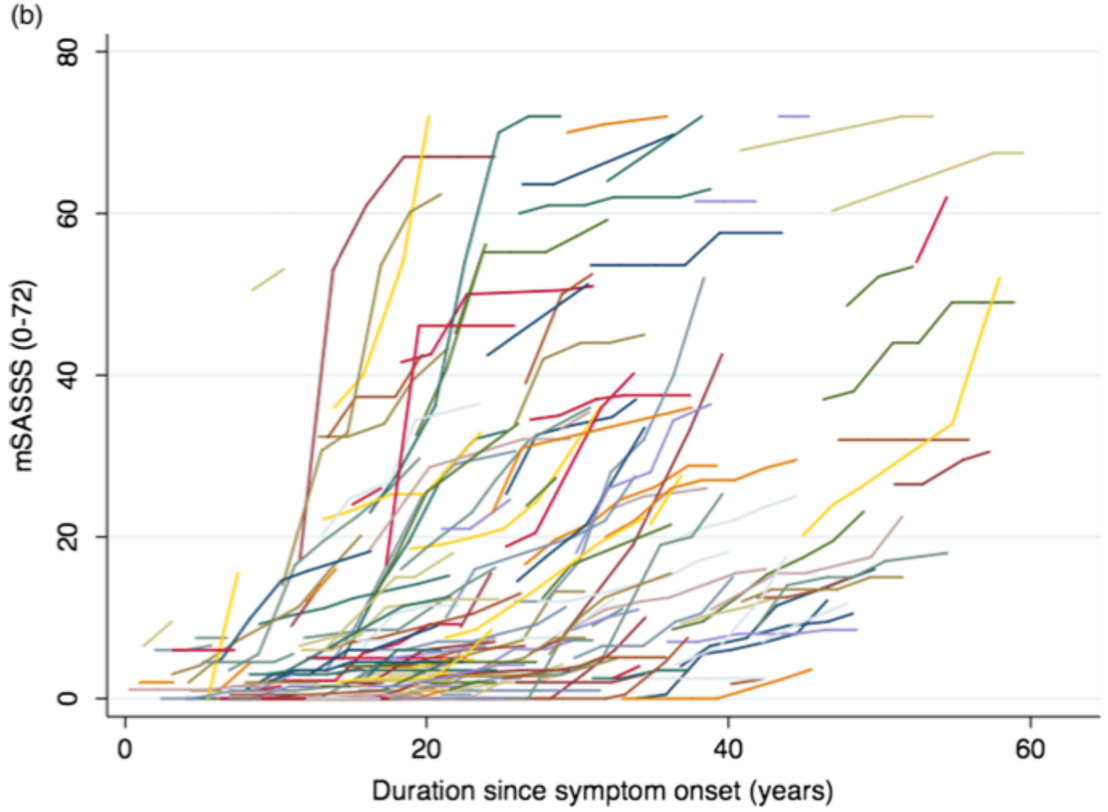
*Net progression, calculated (or recalculated) according to Approach 2 (for details, see Section 2 of the paper).

AS: ankylosing spondylitis; ASAS: the Assessment of SpondyloArthritis international Society; axSpA: axial spondyloarthritis; ESSG: European Spondylarthropathy Study Group; CRP: C-reactive protein; HLA-B27: human leukocyte antigen B27; ILBP: inflammatory low back pain. MRI: magnetic resonance imaging; nr-axSpA: non-radiographic axial spondyloarthritis; r-axSpA: radiographic axial spondyloarthritis; SpA: spondyloarthritis; uSpA: undifferentiated spondyloarthritis.

rate of progression from nr-axSpA to r-axSpA (AS) is 10–40% over 2–10 years

Protopopov Exp Rev Clin Immunol 2018

Disease course in axSpA/AS is highly variable

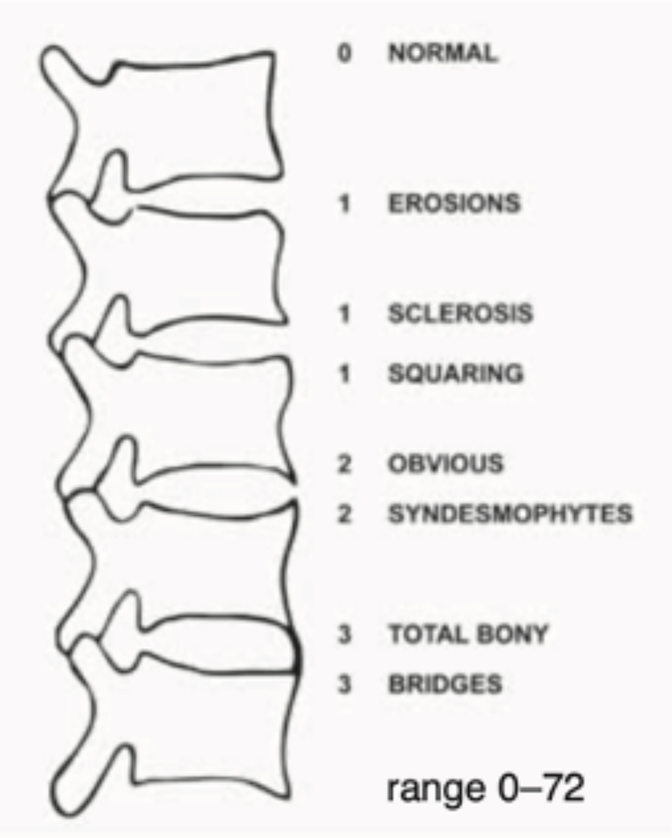


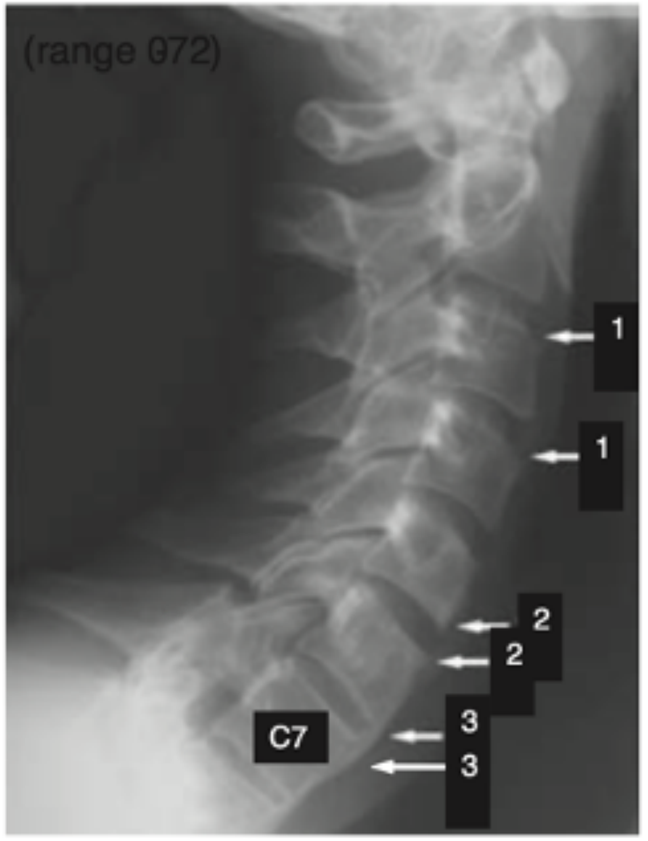
Risk factors for radiographic progression

- Male
- HLA-B27
- High CRP
- Smoking
- Syndesmophytes at baseline

Ramiro Ann Rheum Dis 2015; 74:52-9

Spinal radiographic progression in AS is measured using the mSASSS

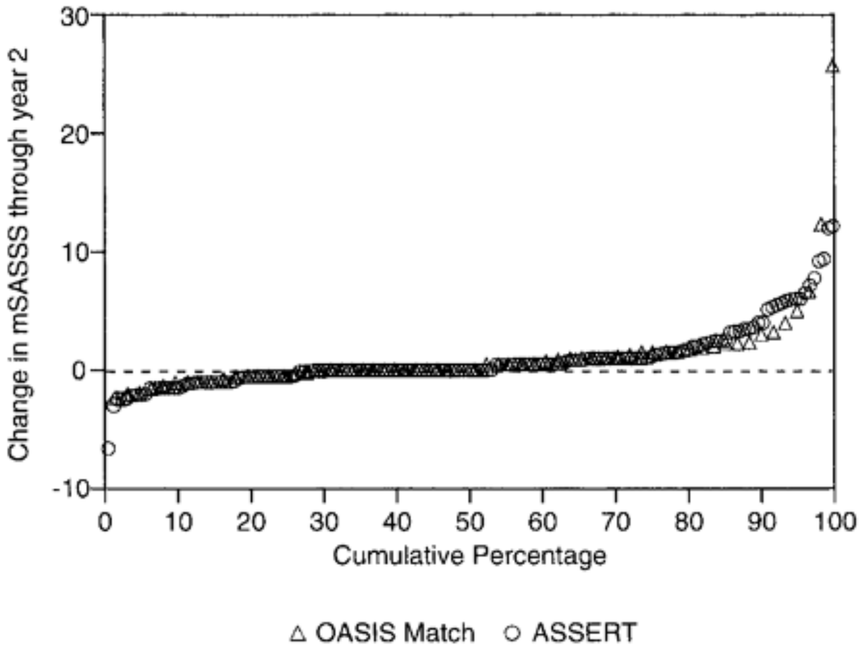




Creemers M et al. Ann Rheum Dis 2005; 64(1): 127-9

Braun Ann Rheum Dis 2011; 70: i97-103

No benefit of TNF inhibition on radiographic progression in early RCTs

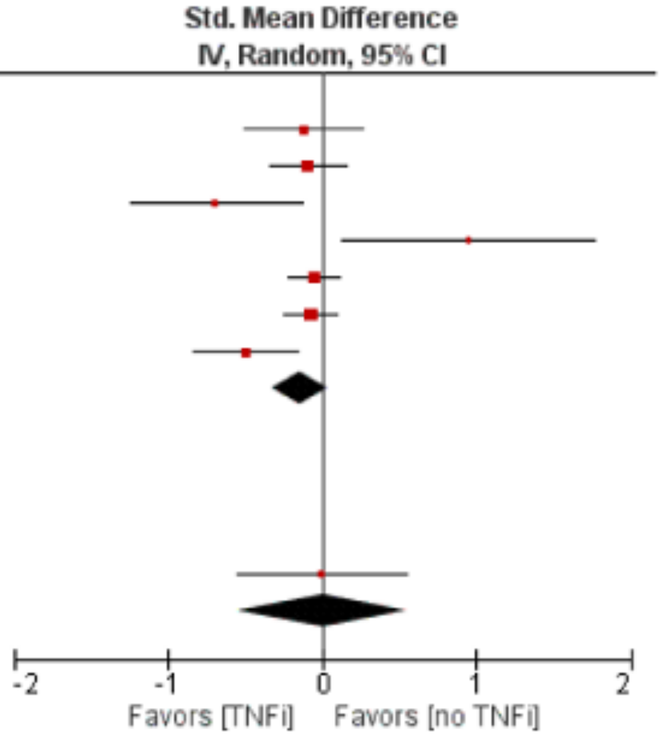


- Infliximab in AS (ASSERT)
  2-year open later extension
- ASSERT vs. OASIS cohort
  no difference in ΔmSASSS over 2 years
- similar results in studies comparing
  Etanercept and Adalimumab with OASIS

van der Heijde Arthritis Rheum 2008; 58: 3063-70

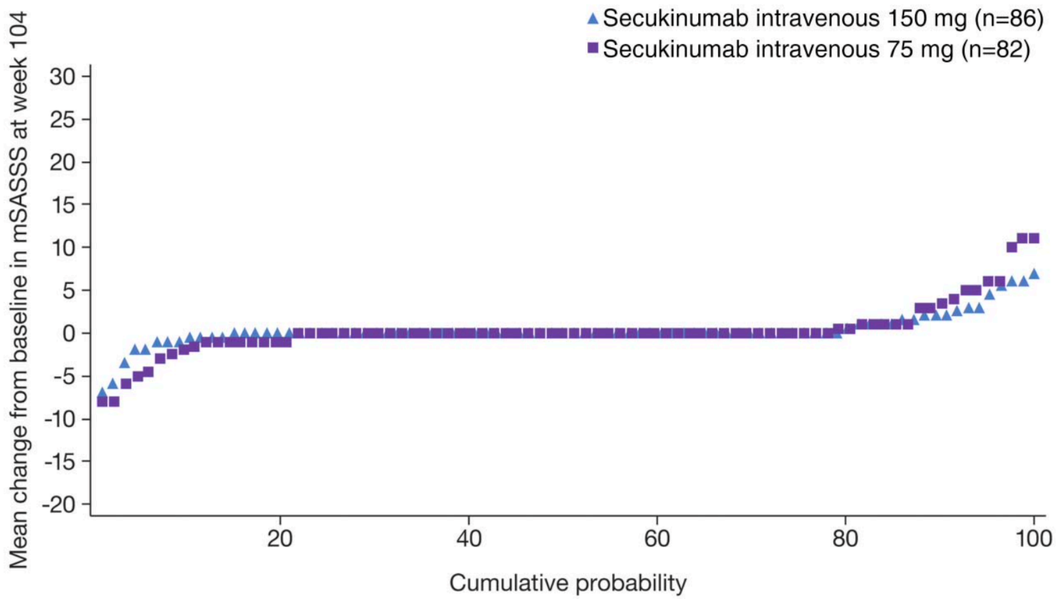
Long-term studies (≧4 years of TNFi therapy) indicate benefit over placebo

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
mSASSS				
Baraliakos 2007	-0.12	0.194	11.3%	-0.12 [-0.50, 0.26]
Braun 2014	-0.09	0.13	16.5%	-0.09 [-0.34, 0.16]
Baraliakos 2014	-0.69	0.283	6.9%	-0.69 [-1.24, -0.14]
Min 2014	0.95	0.418	3.7%	0.95 [0.13, 1.77]
Kim 2016	-0.05	0.082	21.2%	-0.05 [-0.21, 0.11]
Gensler 2018	-0.07	0.088	20.6%	-0.07 [-0.24, 0.10]
Park 2019	-0.49	0.173	12.8%	-0.49 [-0.83, -0.15]
Subtotal (95% CI)			**93.0%**	**-0.14 [-0.32, 0.05]**
Heterogeneity: Tau² = 0.03; Chi² = 16.22, df = 6 (P = 0.01); I² = 63%				
Test for overall effect: Z = 1.48 (P = 0.14)				
CT score of facet joints, total spine				
Chung 2015	0	0.281	7.0%	0.00 [-0.55, 0.55]
Subtotal (95% CI)			**7.0%**	**0.00 [-0.55, 0.55]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.00 (P = 1.00)				



Karmacharya Arthritis Rheumatol 2020; 72:722-49, Boers Rheumatology 2019; 58: 1907-22, Ajrawat Int J Rheum Dis 2020; 23:728-43

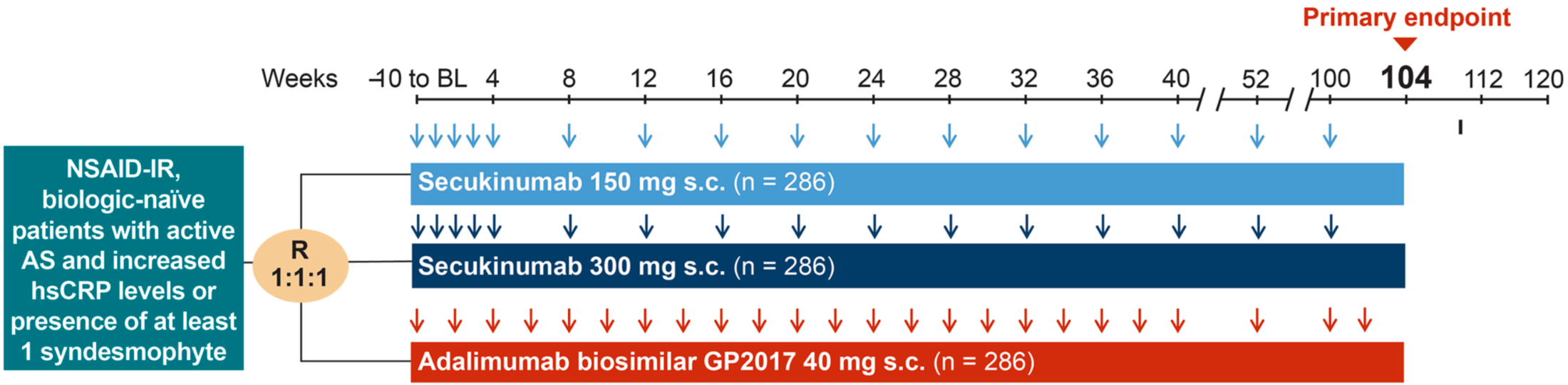
IL-17A inhibitors: limited data on radiographic progression



- Longterm extension of MEASURE 1
  Secukinumab 75 or 150 mg monthly
- ΔmSASSS from baseline to year 1

Braun Ann Rheum Dis 2017; 76:1070-77

SURPASS - first RCT in AS with radiographic primary endpoint (results expected for 2022)



Baraliakos Drug Invest 2020; 40:269-78

Treatment of axSpA/AS - FAQs

1. Am I going to be crippled?
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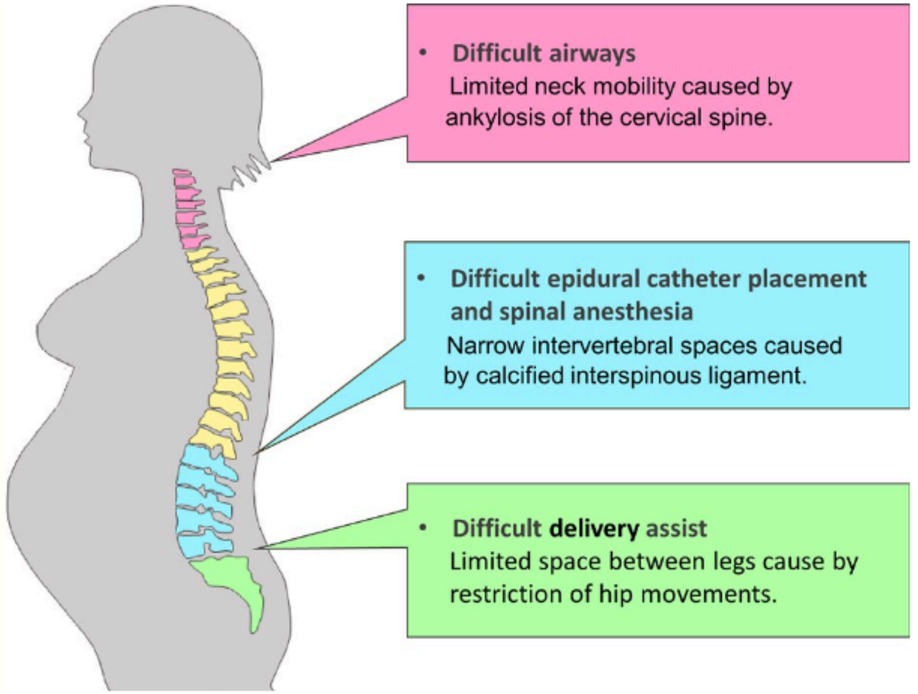
Pregnancy and axial SpA/AS

- limited data, mostly on AS
- disease activity stable or sightly worse during pregnancy
  postpartum flares are common
- Slightly increased risk for premature birth,
  C section, small gestational age, preeclampsia
- Problems in advanced AS
  - difficult airways
  - difficult spinal anesthesia
  - difficult delivery (reduced hip mobility)



Hamroun Rheumatology 2021, Mokbel Clin Rheumatol 2021, Midorikawa Clin Case Rep 2019; 7:766-69

Genetic risk for the development of axSpA

- axSpA/AS has a high degree of heritability
  - AS concordance rate in monozygotic twin 63%
  - AS concordance rate in dizygotic twins 24%
- relative risk in 1st degree relatives of AS patients ~10%
  - increased risk for axSpA/AS in children of axSpA/AS patients
  - chance for not developing axSpA/AS >> chance for developing axSpA/AS
- 6.1% of US population are HLA-B27+
  ~5% of HLA-B27+ individual develop axSpA/AS
  → no screening for HLA-B27 in absence of symptoms

Brown Ann Rheum Dis 2000; 59;883-6, Reveille Arthritis Rheum 2012; 64:1407-11

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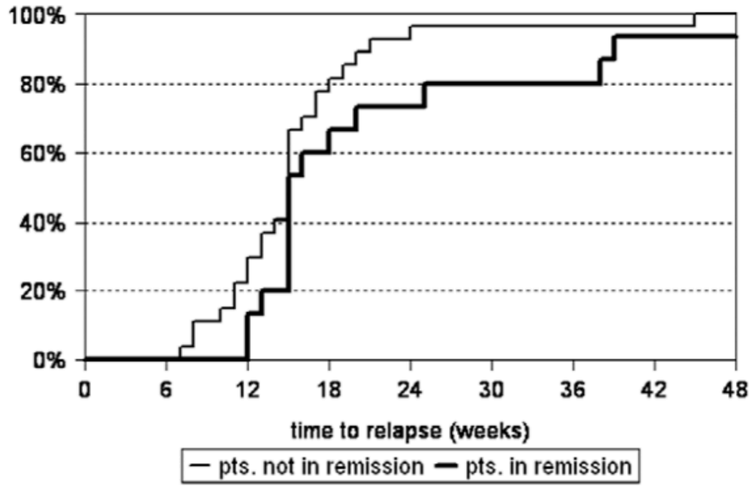
Can drug-free remission be achieved?

Infliximab

AS, open label, n=42



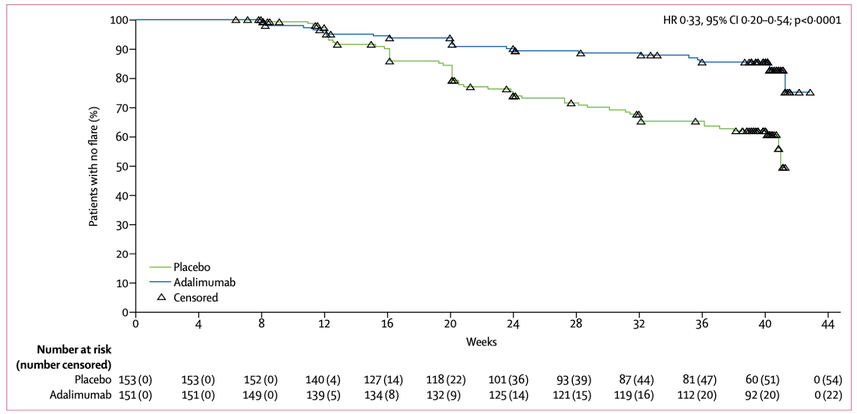
no relapse at week 55
2.4%

Baraliakos Arthritis Res Ther 2005; 7:R439-44

Can drug-free remission be achieved?

Adalimumab
ABILITY-3

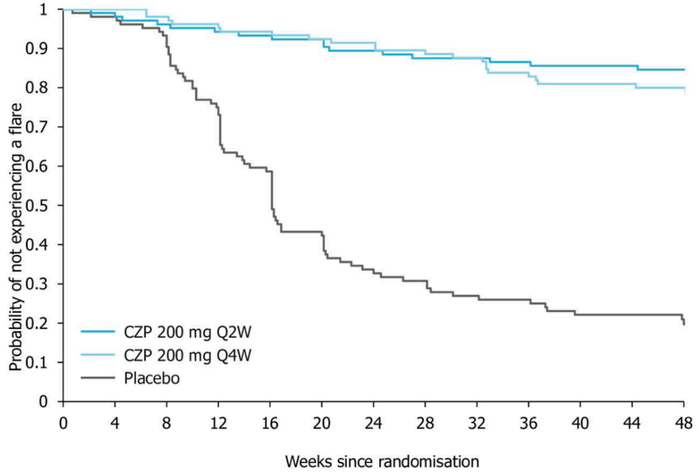
nr-axSpA, RCT, n=305



no flare on placebo at week 40
47%

Certolizumab
C-OPTIMISE

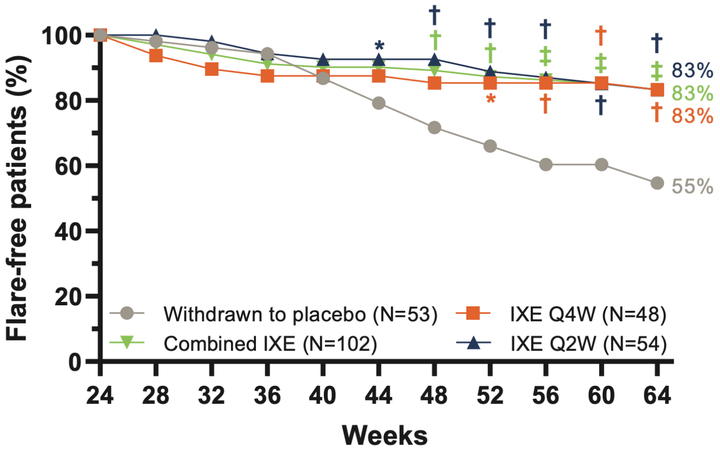
axSpA, RCT, n=313



no flare on placebo at week 48
17.9% r-axSpA
22.9% nr-axSpA

Ixekizumab
COAST-Y

axSpA + AS, RCT, n=741



no flare on placebo at week 40
54.7%

Landewe Lancet 2018; 392:134-144, Landewe Ann Rheum Dis 2020; 79:920-928; Landewe Ann Rheum Dis 2021

Treatment of axSpA/AS - FAQs

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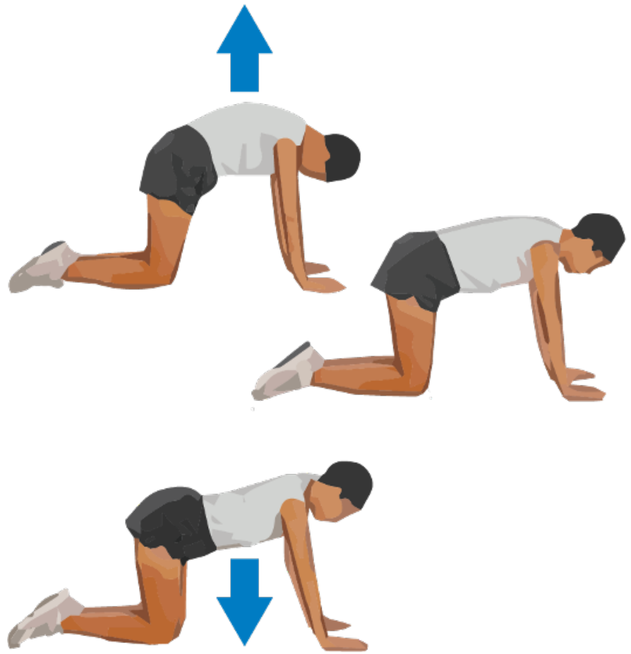
Physical therapy and exercise

- proven benefits on patient symptoms and wellbeing, often neglected
  strong recommendation for PT over no PT in ACR/SAA/SPARTAN guidelines
- important in all phases of the disease, most important in AS
- implement exercise program at diagnosis, initially with physical therapist, focus on:
  - spinal mobility
  - deep breathing exercises
- instructions on proper posture and gait:
  - firm mattress without/with thin pillow
  - walk erect
  - avoid prolonged stooping or bending
- regular physical activity for general health + well-being,
  avoid high impact activities if ankylosis/osteoporosis present



“Can I change my diet instead of injecting drugs?”

- Proposed interventions:
  - fasting
  - low starch or gluten-free diet
  - probiotics
  - vitamin supplements
  - …
- SLR by Macfarlane et al. 2018
  - 10 full-text articles, none from US or Canada
  - “little evidence regarding the fact that aspects of diet influence the severity of AS or are part of its etiology”
  - scarce literature, methodological flaws

Macfarlane Eur J Rheumatol 2018; 5:45-52

Treatment of axSpA/AS - FAQs

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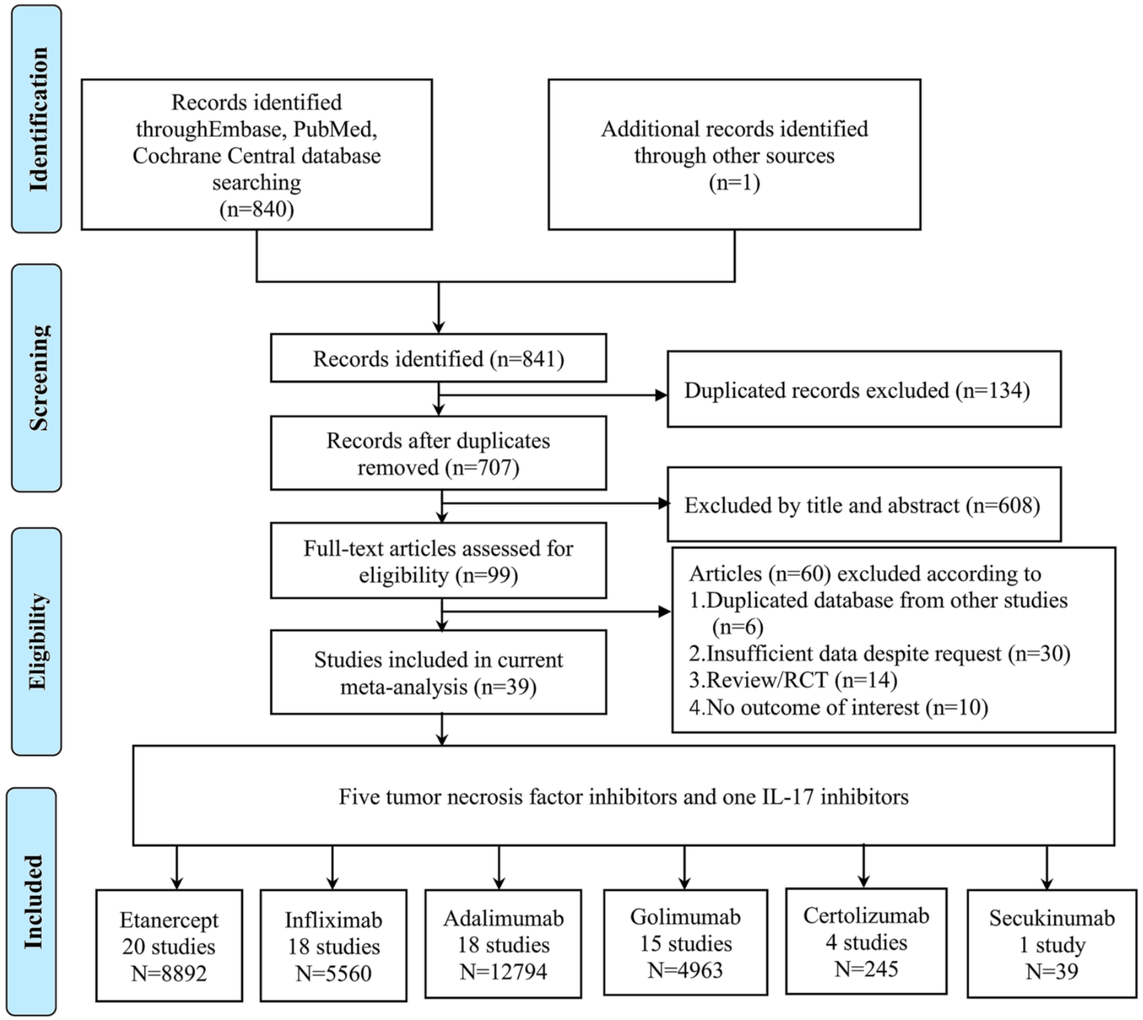
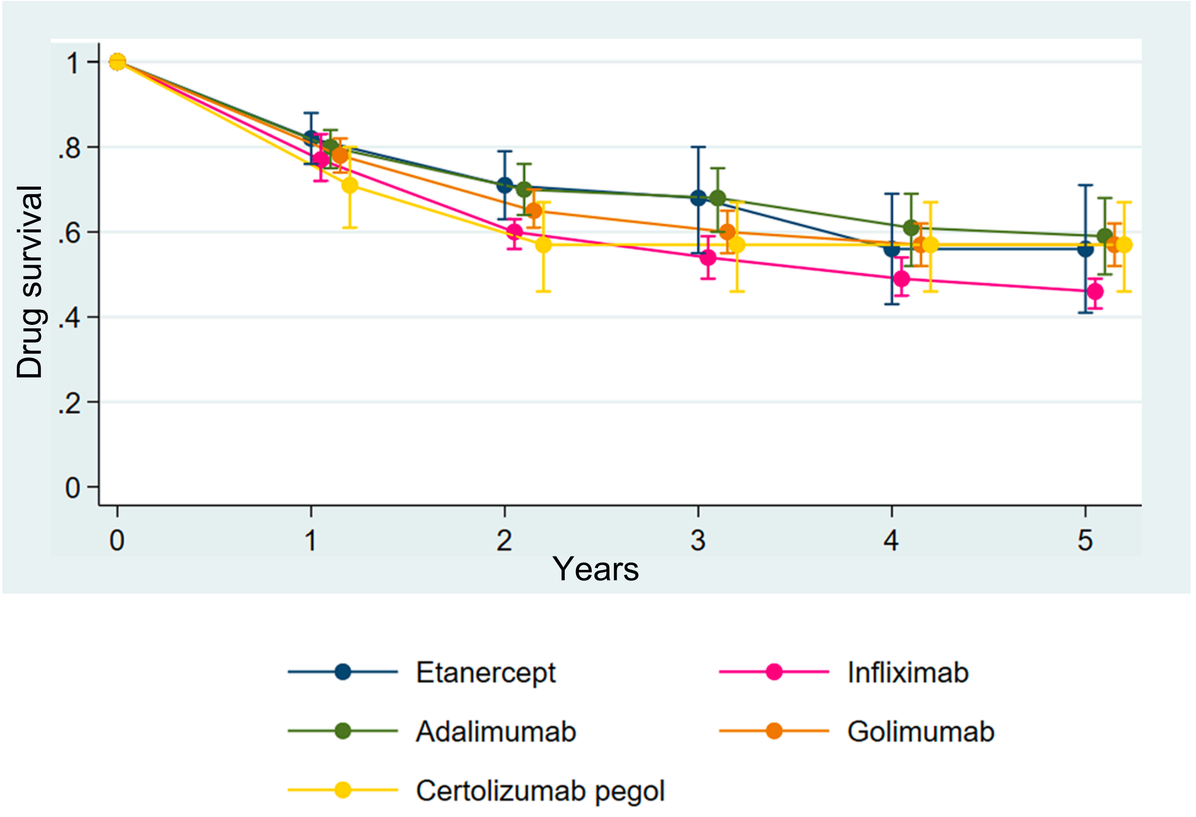
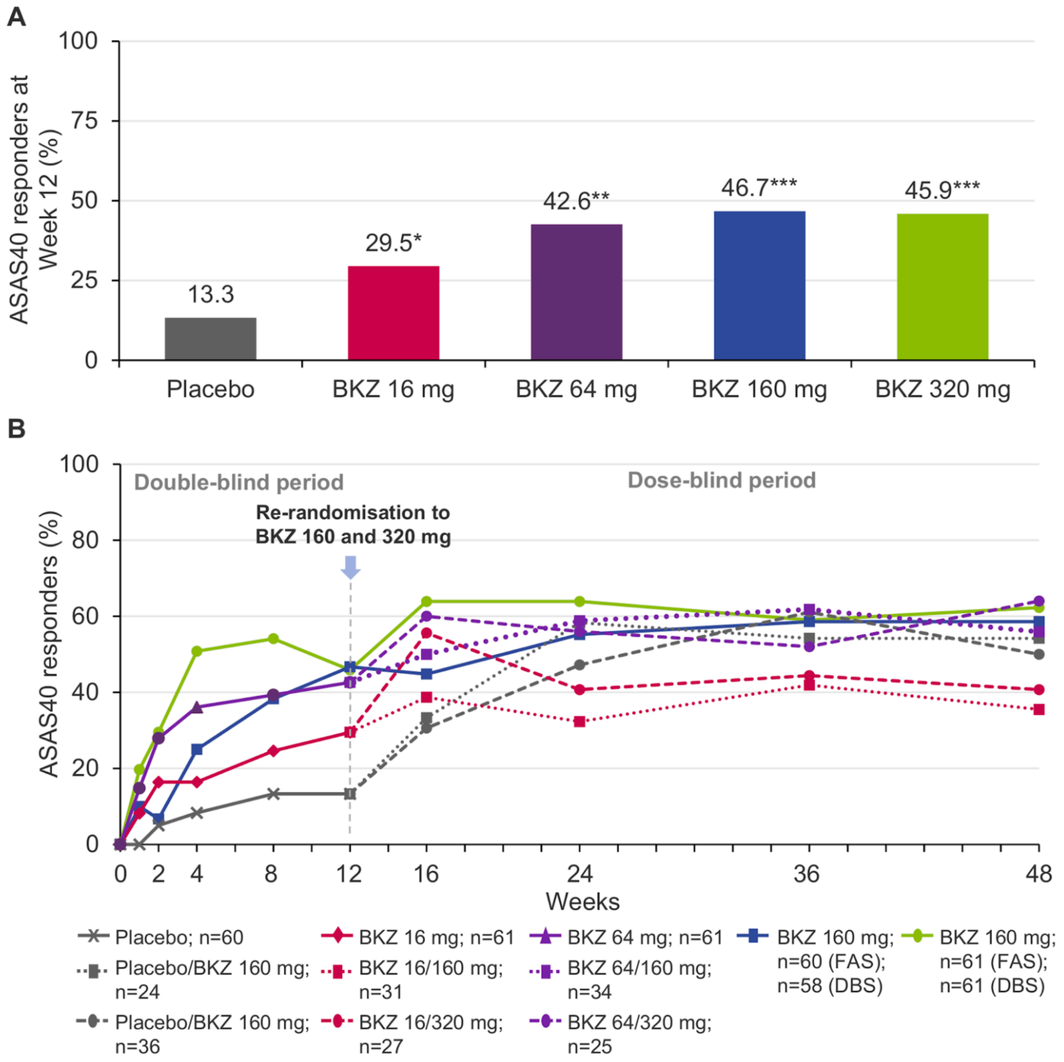
TNFi drug survival in AS ~80% at 1 year





Yu BioDrugs 2020; 34:669-679

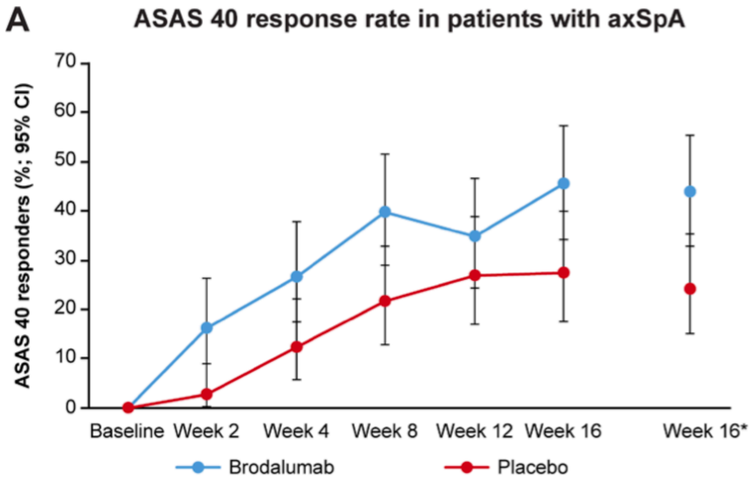
Bimekizumab in active AS, phase IIb RCT

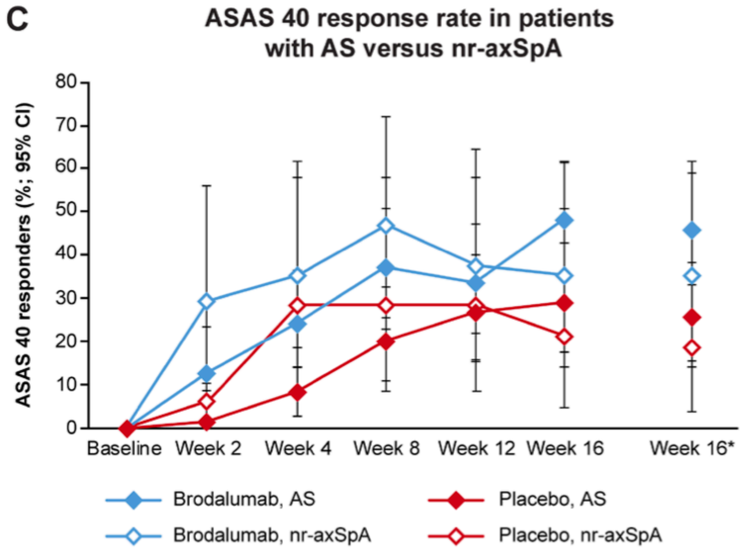


- AS, n=303
  1:1:1:1:1 Bimekizumab 16, 64, 160, 320 mg vs. placebo
- Primary endpoint ACR40 at week 12
  29.5 - 46.7% vs. 13.3%, $p<0.05$
- Candida infection 7.5% vs. 0%

van der Heijde Ann Rheum Dis 2020; 79:595-604

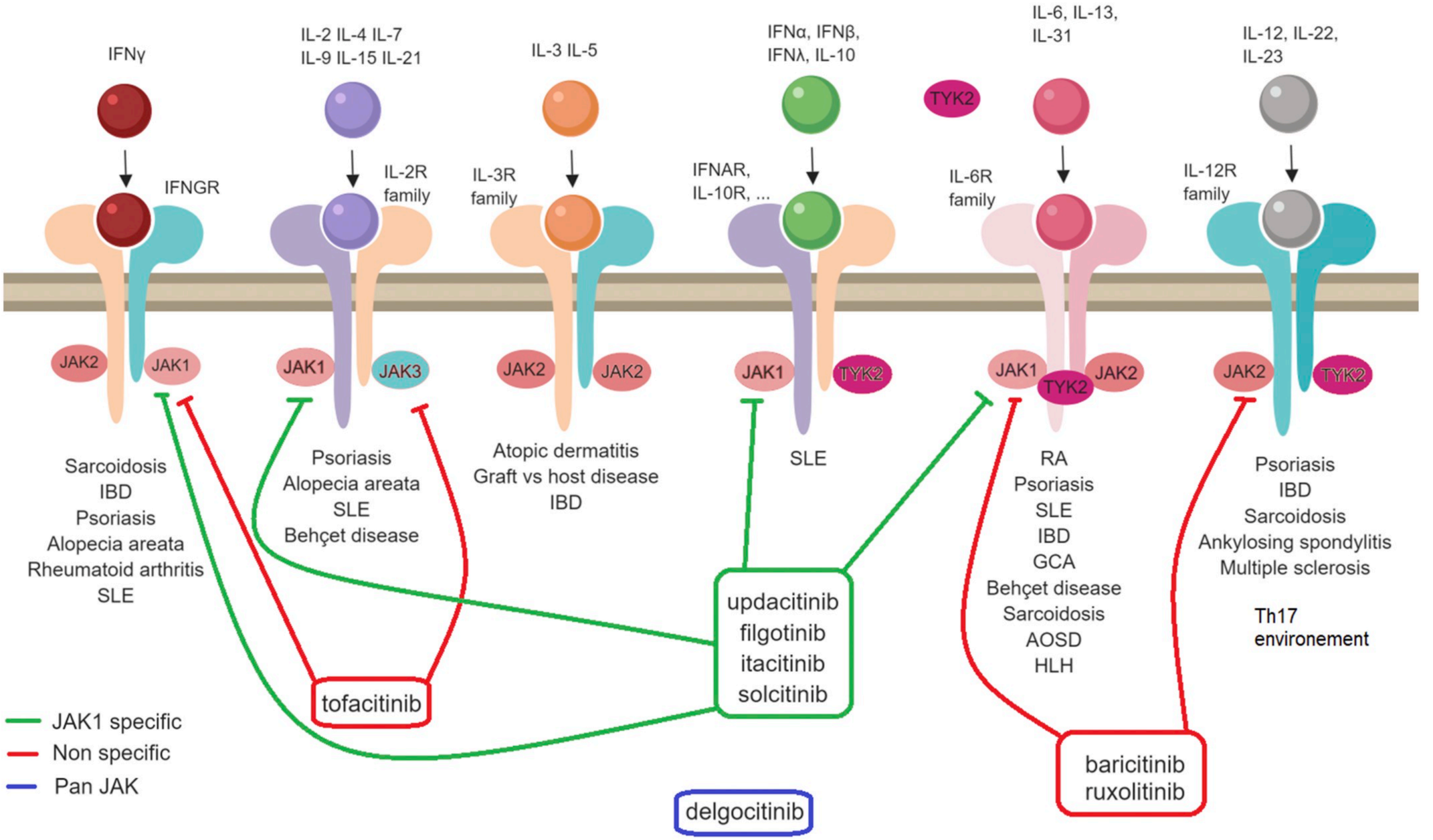
Brodalumab in active axial SpA, phase III RCT





- Active axial SpA, n=159
  (79% AS, 21% nr-axSpA)
- Primary endpoint ACR40 at week 16
  43.8% vs. 24.1%, p=0.018
- Effect size similar to studies with
  Secukinumab, Ixekizumab
- No new safety signals

Wei Ann Rheum Dis 2021



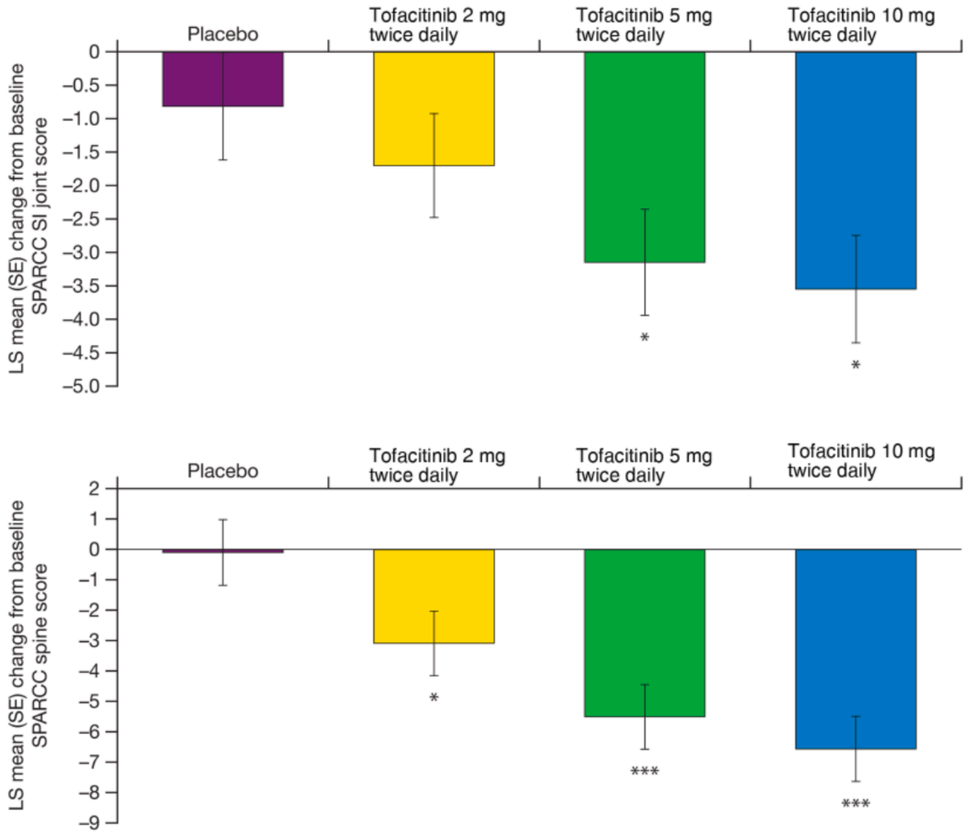
Jamilloux Autoimmun Rev 2019; 18: 102390

JAK inhibitors - promising results in clinical trials

Tofacitinib, phase II
AS

Table 2 Primary efficacy endpoint results: ASAS20 response rate at week 12

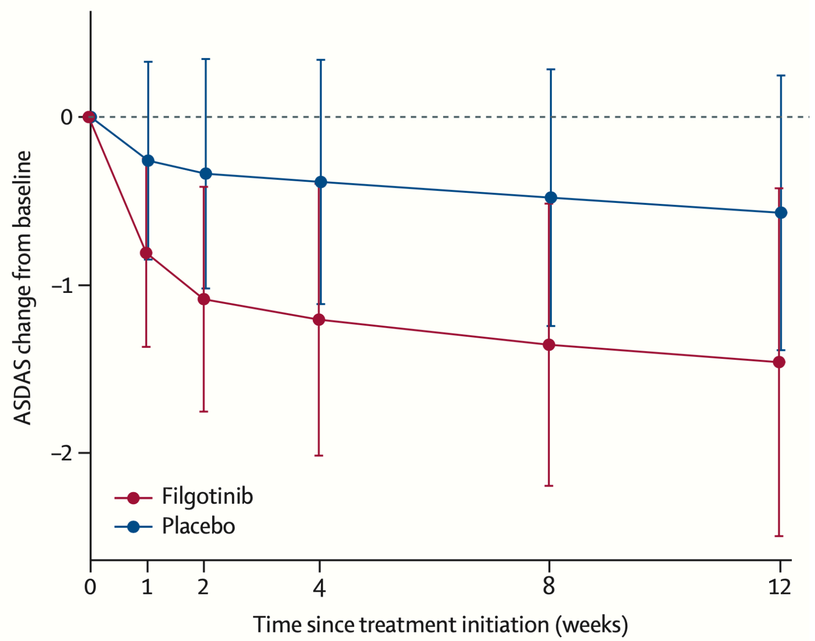
	Placebo N=51	Tofacitinib 2 mg twice daily N=52	Tofacitinib 5 mg twice daily N=52	Tofacitinib 10 mg twice daily N=52
Emax model-predicted ASAS20 response, %†	40.1	56.0	63.0	67.4
Estimated treatment difference from placebo	–	15.8	22.9	27.3
95% credible interval	–	5.0, 30.3	8.4, 37.7	10.7, 43.4
60% credible interval	–	10.2, 21.2	16.5, 29.3	20.3, 34.4
50% credible interval	–	11.1, 19.9	17.8, 28.0	21.8, 33.0
Actual ASAS20 response, %†	41.2	51.9	80.8***	55.8



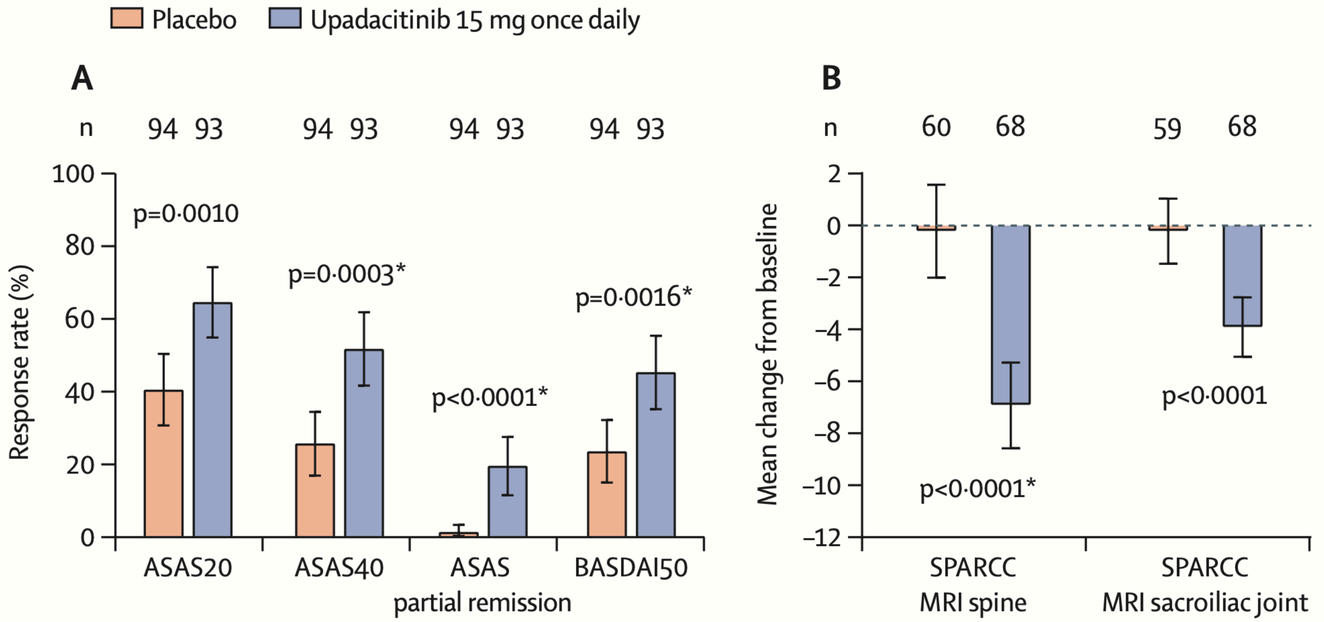
van der Heijde Ann Rheum Dis 2017; 76:1340-7

JAK inhibitors - promising results in clinical trials

Filgotinib, phase II
AS

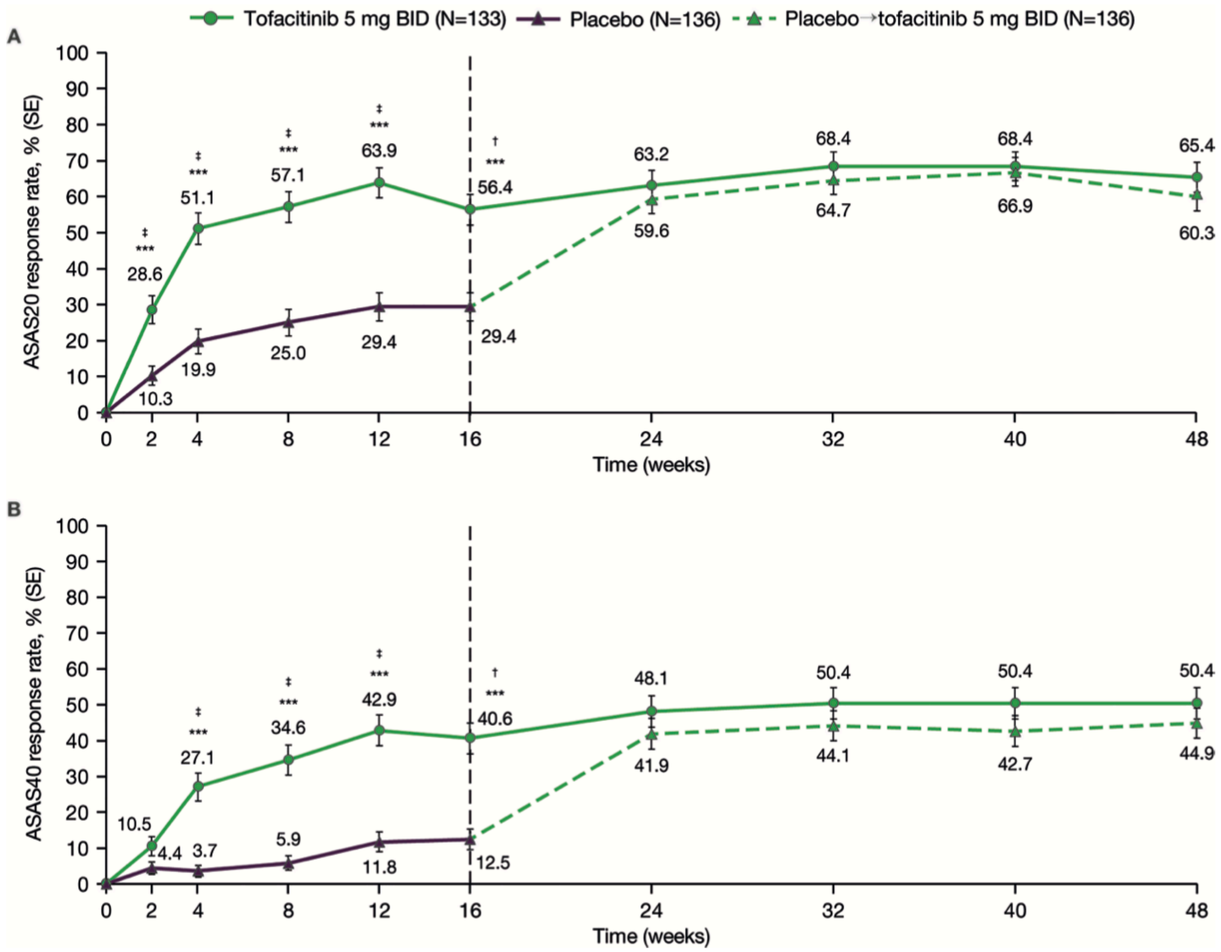


Upadacitinib, phase II/III
AS



van der Heijde Lancet 2018; 392:2378-2387, van der Heijde Lancet 2019; 394:2108-2117

Tofacitinib in active AS - Phase III RCT



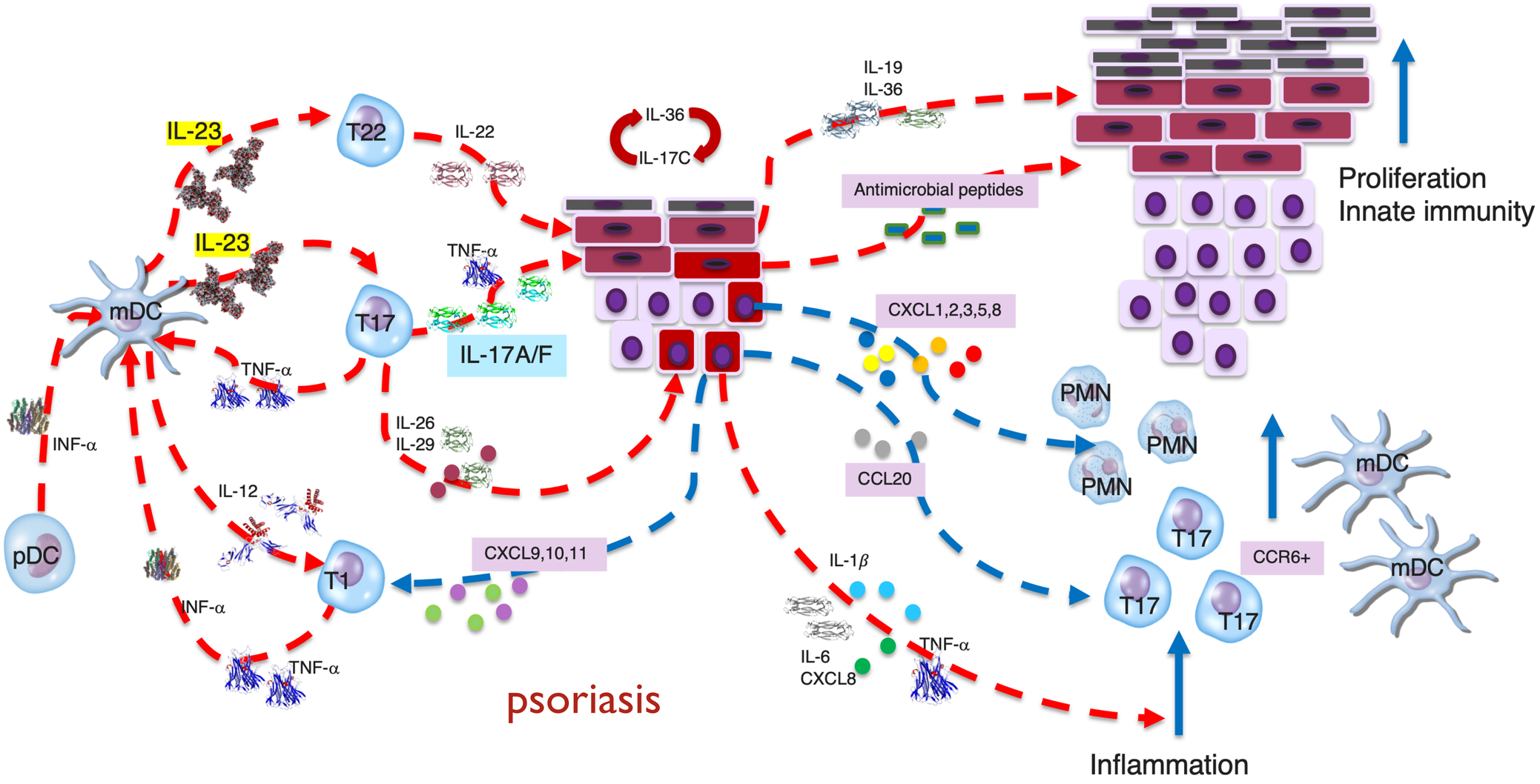
- Tofacitinib 5 mg BID vs. placebo, AS, n=269
- Primary endpoint ACR20 at week 16: 56.4% vs. 29.4%, p<0.0001
- no MACE, thromboembolic events, malignancies, opportunistic infections

Deodhar Ann Rheum Dis 2021

Why do JAK inhibitors work in axSpA/AS ?

cytokine	**TNF**	**IL-17A**	**IL-6**	**IL-23**
receptor	TNFR1 TNFR2	IL-17RA IL-17RC	IL-6R GP130	IL-12RB1 IL-23R
signaling pathway	NFκB MAPK apoptosis	NFκB MAPK	JAK/STAT (JAK1, JAK2)	JAK/STAT (JAK2, TYK2)
efficacy of biologic inhibitors	++	++	-	-

What is next in axSpA/AS therapy?



Courtesy Lluis Puig

Summary

- NSAIDs, TNF and IL-17A inhibitors are established therapies in axial SpA/AS, biologics likely inhibit radiographic progression with prolonged therapy
- biomarkers are needed
  - determine optimal first line drug target
  - identify candidates for drug discontinuation
- clinical trials of IL-23 inhibitors failed,
  IL-23 may play a critical role early but not in established disease
- JAK inhibitors have shown efficacy in clinical trials,
  despite uncertainty about targeted cytokine receptor pathway,
  regulatory approval likely → welcome oral treatment option

SpADE BaxSpA

Joerg Ermann, MD
Brigham and Women's Hospital
Harvard Medical School
jermann@bwh.harvard.edu