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Is There an NP in the Rheum?

The Role of Nurse Practitioners in Overcoming Underrecognition and Treatment Delays to Improve Patient Outcomes in Axial Spondyloarthritis

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Angela L. Borger, DNP, FNP-BC, DNC, has no real or apparent conflicts of interest to report.

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Learning Objectives

- Outline methods for differentiating between mechanical and inflammatory back pain using ASAS classification criteria for axial spondyloarthritis (axSpA) as well as clinical presentation, laboratory studies, and appropriate imaging
- Explain how axSpA manifests differently in women in order to facilitate a timelier diagnosis and avoid worsening symptoms
- Discuss how to manage the extra-articular manifestations and quality-of-life concerns that are common in patients with axSpA
- List the guideline recommendations and clinical trial evidence for the management of axSpA

ASAS, Assessment of SpondyloArthritis International Society.

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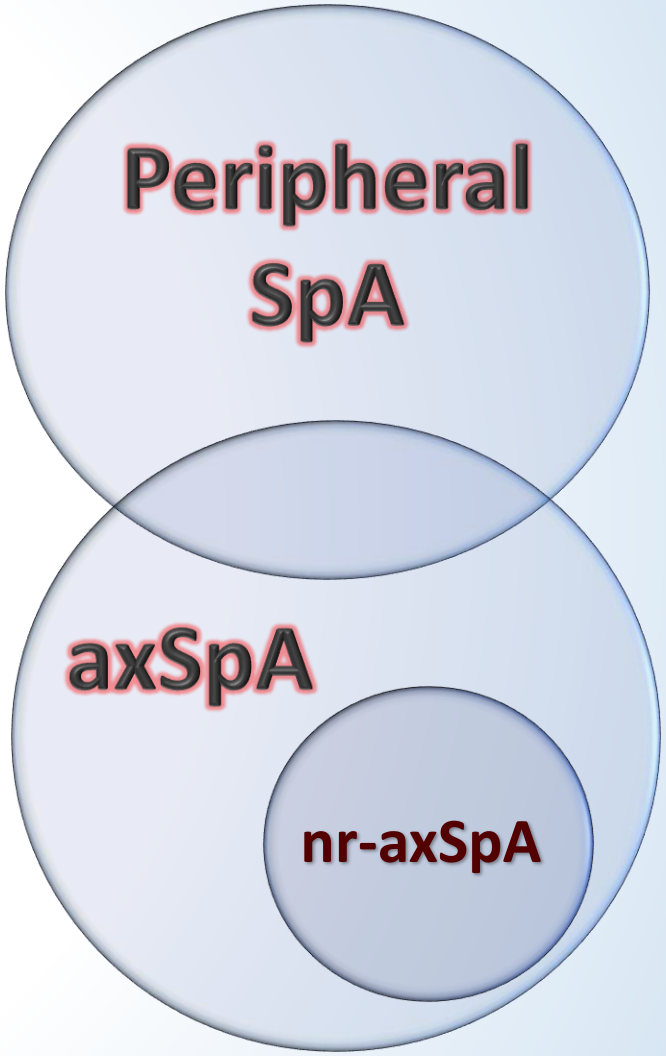
axSpA: What Is It and Who Has It? Epidemiology, Comorbidities, and Quality of Life

Defining the 2 Main Categories of axSpA

1. **r-axSpA** = radiographic evidence of sacroiliitis, more commonly known as AS
2. **nr-axSpA** = ***no*** radiographic evidence of sacroiliitis
   - Both: Inflammatory arthritis of the spine with a heterogeneous presentation
   - Chronic back pain the most common symptom

- Peripheral SpA: Signs are predominantly peripheral rather than axial
  - Includes inflammatory arthritis
  - ~30% of patients with axSpA have asymmetric inflammation in peripheral joints



AS, ankylosing spondylitis; nr-axSpA, nonradiographic axial spondyloarthritis; r-axSpA, radiographic axial spondyloarthritis.

Magrey MN, et al. *Mayo Clin Proc*. 2020;95:2499-2508; van der Heijde D, et al. *Ann Rheum Dis*. 2017;76:978-991.

2 Main Categories; 1 Disease Continuum

Current thinking is that axSpA is a **single disease *continuum***, with ***radiographic severity that increases over time***

nr-axSpA	AS (r-axSpA)
• No radiographic evidence of sacroiliitis • Inflammation of sacroiliac joints may be detected by MRI • Symptom severity usually less than with AS	• Evidence of sacroiliitis on radiographs (ie, x-rays) • Spinal involvement is more extensive • Structural vertebral abnormalities are often present

nr-axSpA Patients

5%–10% develop AS within 2 years

20% develop AS within 5 years

Radiographic evidence of AS

MRI, magnetic resonance imaging.

Sieper J, van der Heijde D. *Arthritis Rheum*. 2013;65:543-551; van der Heijde, et al. *Ann Rheum Dis.* 2017;76:978-991.

Epidemiology of axSpA

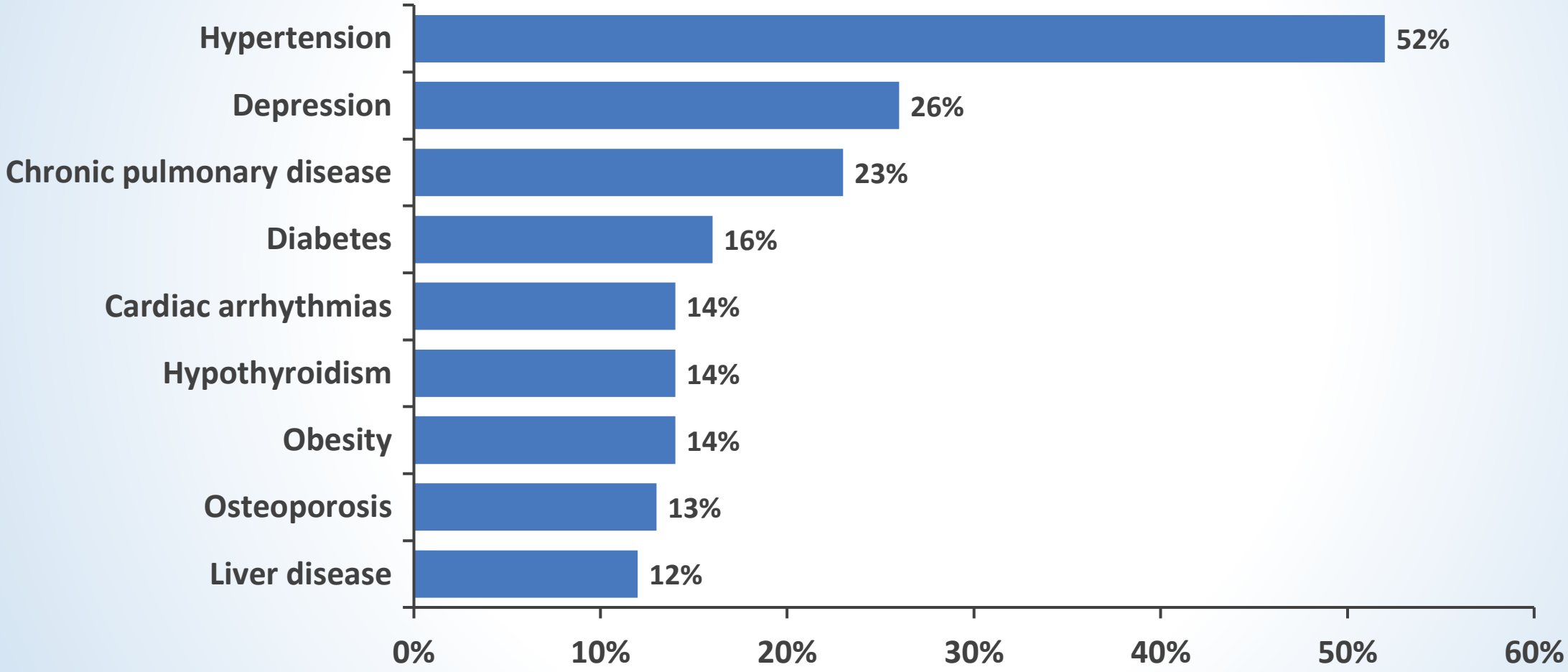
- **Prevalence:** Affects up to 1.4% of Americans (~4.6 million)*[1-3]
- **Men vs women:** AS more common in men than women (3:1 ratio)[4]
  - nr-axSpA equally prevalent between men and women[5]
  - Women have overall poorer function and quality of life[5]
- **Age:** Symptom onset before age 45 in 92% of cases, worldwide[6]
  - Median age of onset 26 years[6]; lower mean age of 22 for women[7]
  - Rare onset after age 50[6]
- **Ethnicities:** More common in non-Hispanic Caucasians and Mexican Americans (both 1.5%) vs African Americans (0.9%)[7]
- **Genes:** ~26% of people with affected 1st-degree relative[8]

*1.4% of total population of 331,449,281 in 2020 per US Census Bureau.

1. Reveille JD, et al. *Arthritis Care Res (Hoboken)*. 2012;64:905–910. **2**. Strand V, Rao SA, Shillington AC, et al. *Arthritis Care Res (Hoboken).* 2013;65:1299-1306.
2. **3**. Epstein B, Lofquist D. US Census Bureau. Accessed May 18, 2022. https://www.census.gov/library/stories/2021/04/2020-census-data-release.html
3. **4**. Rusman T, et al. *Scand J Rheumatol*. 2021 Nov 2:1-7. [Online ahead of print]. **5**. Wright GC, et al. *Semin Arthritis Rheum*. 2020;50:687-694. **6**. Boel A, et al. *Rheumatology*. 2022;61:1468-1475. **7**. Danve A, Deodhar A. *Clin Rheumatol*. 2019;38:625-634. **8**. van der Linden S, et al. *Ann Rheum Dis*. 2022;81:831-837.

axSpA-Associated Conditions and Comorbidities

Population-based study of 21,892 patients in insurance database (1,776 with axSpA)



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Redeker I, Callhoff J, et al. *Arthritis Res Ther*. 2020;22:210.

axSpA = Worse Quality of Life (QOL)

- QOL analysis of 1,810 people with axSpA
- 2 main factors drive poor QOL
  - Active disease
  - Worse/reduced physical function
- These contribute to
  - Pervasive fatigue
  - Sleep disturbance
  - Mood disorders (depression/anxiety)
  - Widespread pain

Macfarlane GJ, et al. *Ann Rheum Dis.* 2020;79:202-208.

axSpA Hallmark: Back Pain — Differences Between Types

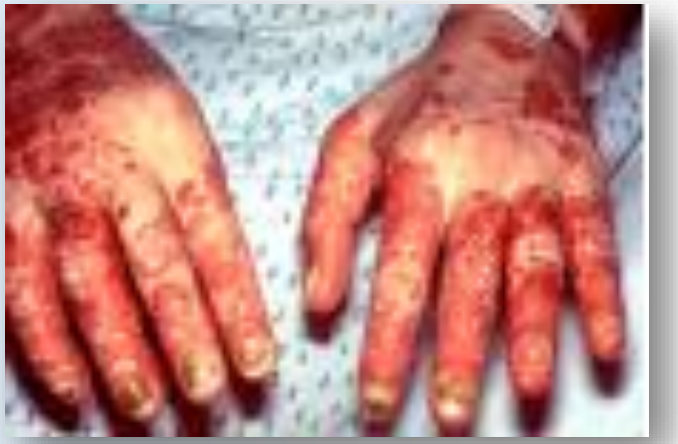
Variable	Inflammatory Back Pain (IBP)	Mechanical Back Pain
Age at onset	<40–45 years	Any age
Rapidity of onset	Insidious (gradually)	Variable, may be acute
Chronicity	>3 months	Variable duration
Night pain	Usually worse at night; pain may cause awakening in latter half of the night	Variable
Effect of movement or physical activity	Pain improves with activity, not rest; not affected by position changes	Pain worsens with activity, improves with rest; may improve or worsen with position changes
Morning stiffness	Persists for >30 minutes; may be severe	Short-lived
Response to NSAIDs	Good response	Variable response
Location and characteristics of pain	Low back pain common but may affect anywhere in the spine; may cause alternating buttock pain; does not radiate into legs; does not cause numbness, burning, or tingling	Anywhere in the spine; may radiate into legs; may cause numbness, burning, or tingling

NSAIDs, nonsteroidal anti-inflammatory drugs.

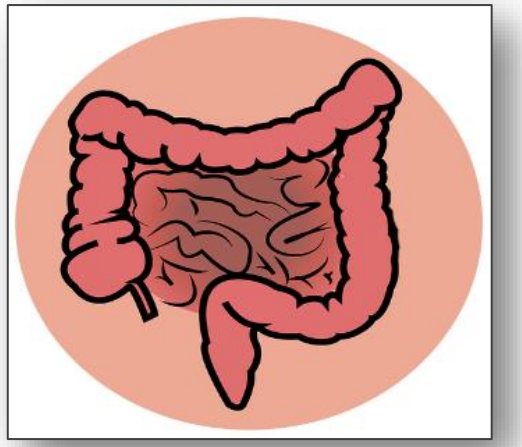
Magrey MN, et al. *Mayo Clin Proc.* 2020;95:2499-2508; van der Heijde D, et al. *Ann Rheum Dis.* 2017;76:978-991.

Extra-Articular Manifestations of axSpA Other Than IBP

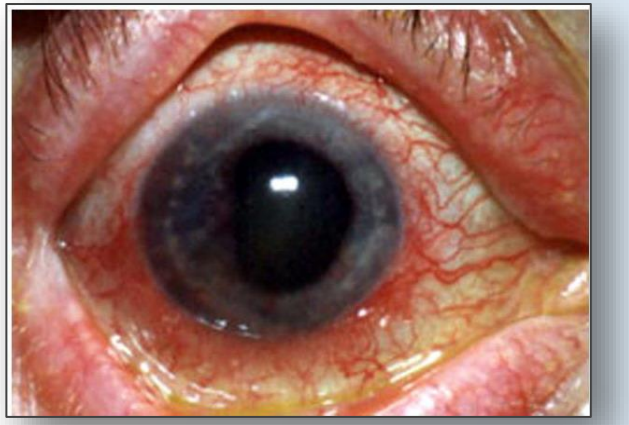
Psoriasis



Inflammatory Bowel Disease



Uveitis



These can sometimes be presenting signs; recognition and referral to specialty care for extra-articular manifestations is essential

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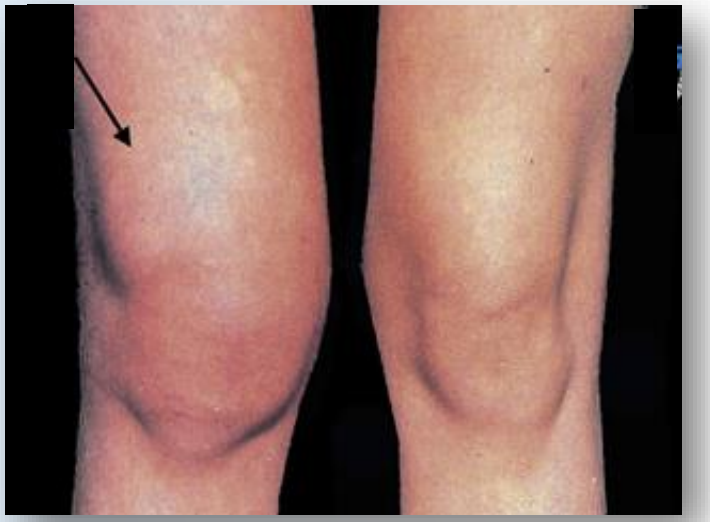
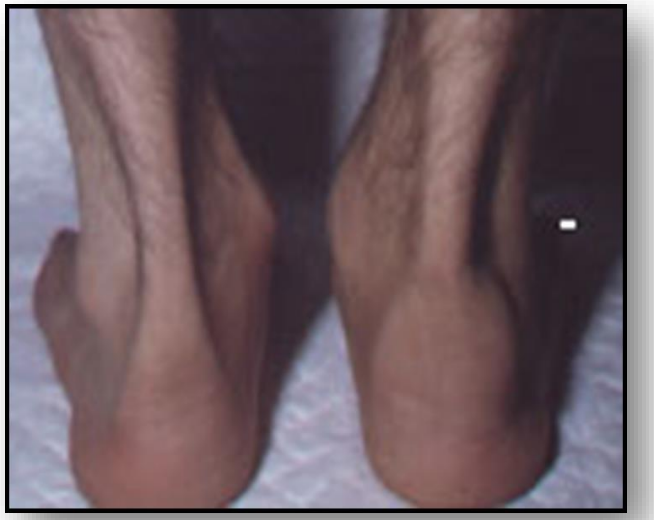
Peripheral Manifestations of axSpA

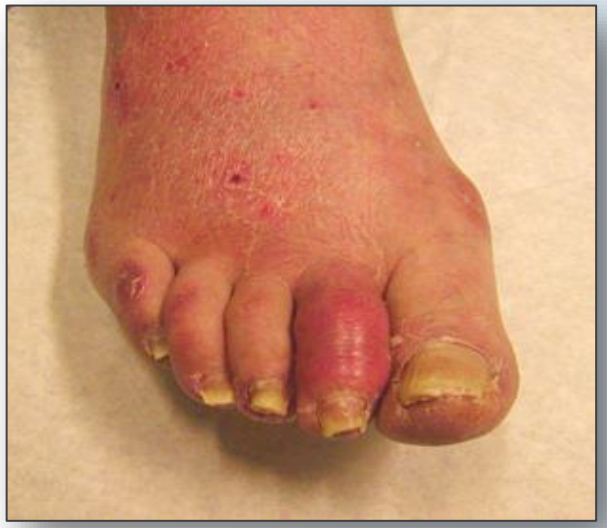
Arthritis



Enthesitis



Dactylitis



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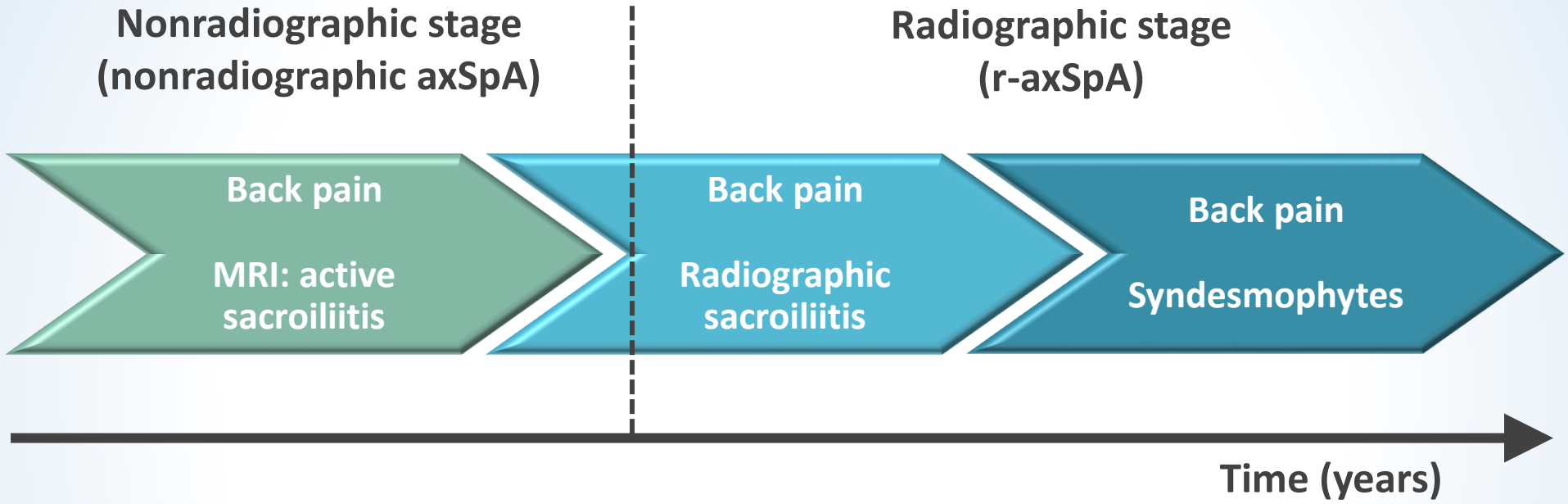
axSpA Diagnostic Challenges and Criteria

nr-axSpA to AS Continuum



- Not all nr-axSpA patients progress to r-axSpA (aka, AS)
- Predictors of progression include disease duration and severity, extent of MRI inflammation, and male gender

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Rudwaleit M, Sieper J. *Nat Rev Rhematol.* 2012;8:262-268.

ASAS Diagnostic Criteria

Back pain ≥3 months and age at onset ≤45 years (with or without peripheral manifestations)

Sacroiliitis on imaging
plus
≥1 SpA feature

or

HLA-B27
plus
≥2 other SpA features

SpA features

- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's/colitis
- Good response to NSAIDs
- Family history of SpA
- HLA-B27
- Elevated CRP

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Rudwaleit M, et al. *Ann Rheum Dis*. 2009;68:777-783.

Diagnostic Delays Common

- Interval between onset of symptoms and ***diagnosis often takes up to 14 years for patients with AS***
- Multiple nuanced presentations mean diagnosis never straightforward
- AS ***rarely*** diagnosed early
- Women experience longer diagnostic delay, ranging from 9–14 years vs 5–7 years in men

Majority of affected people are not yet diagnosed

Danve A, Deodhar A. *Clin Rheumatol*. 2019;38:625-63; Dube CE, et al. *Rheumatol Ther*. 2021;8:1015-1030; Wright GC, et al. *Semin Arthritis Rheum*. 2020;50:687-694.

Other Factors That Contribute to Delay in Diagnosis

- High prevalence of back pain
- Limitation of physical examination
- Lack of specific, unique biomarkers
- Most patients referred to orthopedists, or chiropractors
- No clear guidelines to refer patients to rheumatologists
- Good response to NSAIDs

Danve A, Deodhar A. *Clin Rheumatol*. 2019;38:625-634; Magrey M, et al. *ACR Open Rheumatol*. 2020;2:616-626.

Basis for Diagnosis

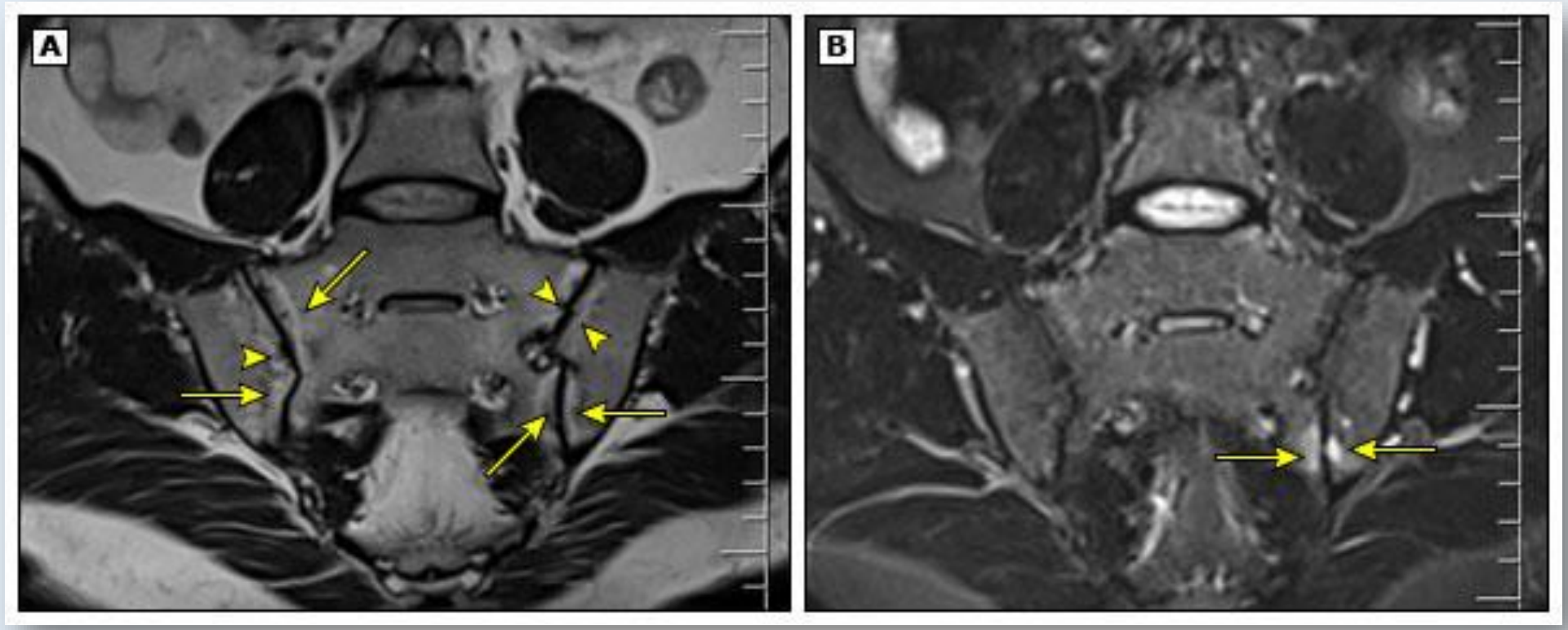
- Diagnosis based on combination of physical exam, history, and imaging
- ***No definitive diagnostic test***
- HLA-B27 protein seen in ~90% of all patients who present with axSpA
  - But . . . HLA-B27 expression in ~8% of general population, most of whom never develop axSpA[4]

Lack of standardization and uniformity results in misclassification and underdiagnosis

Magrey MN, et al. *Mayo Clin Proc*. 2020;95:2499-2508; Ward MM, et al. *Arthritis Care Res (Hoboken)*. 2019;71:1285-1299; Chen B, et al. *Mol Med Rep*. 2017;15:1943-1951; Sieper J, et al. *Best Pract Clin Rheumatol*. 2006;20:401-417.

Guidelines: Imaging Key

ACR/SAA/SPARTAN guidelines, updated in 2019, recommend MRI to ascertain spine and sacroiliac inflammation and treatment response

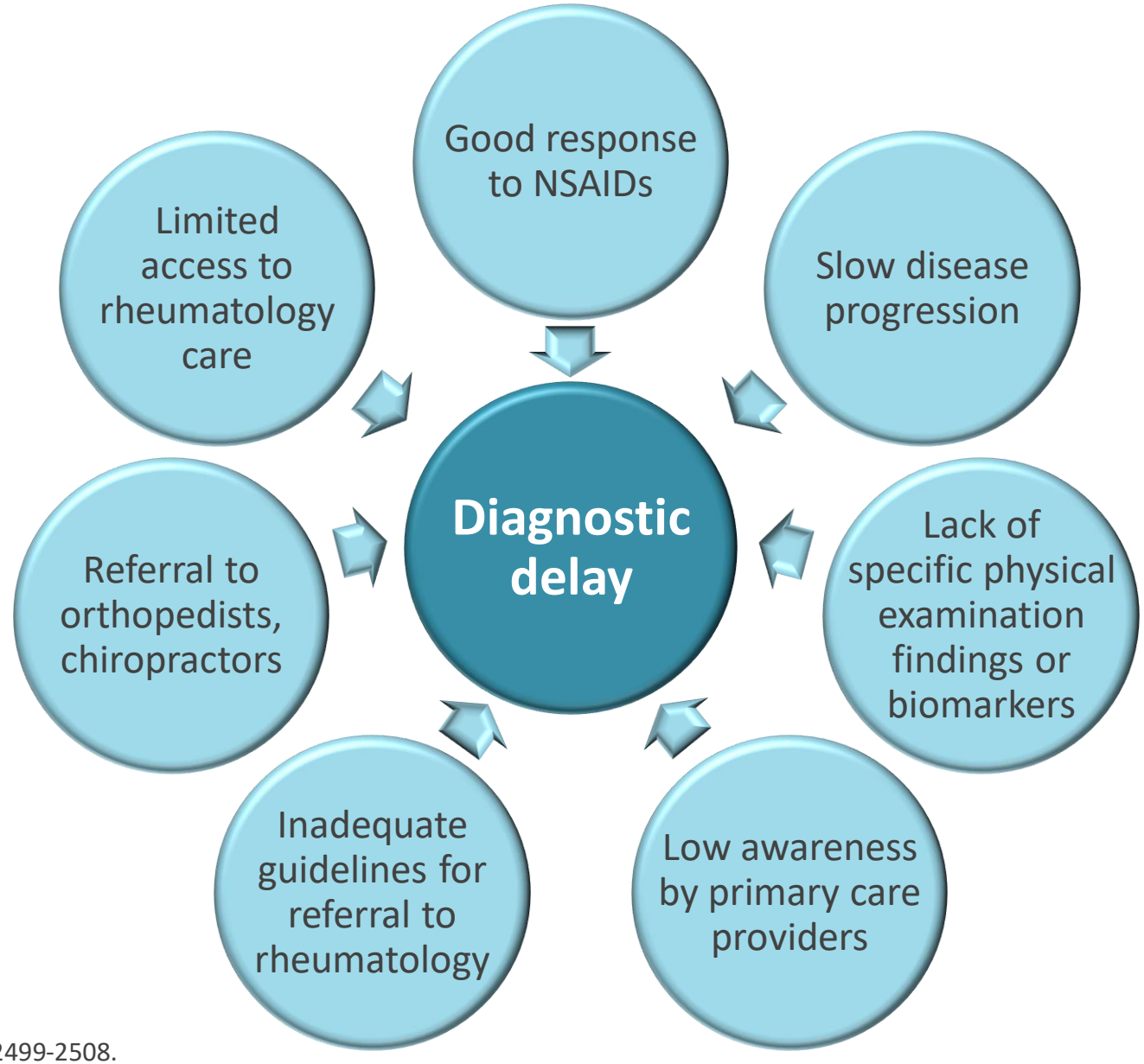


Arrows delineate fatty lesions; arrow heads indicate erosions

Arrows indicate bone marrow edema

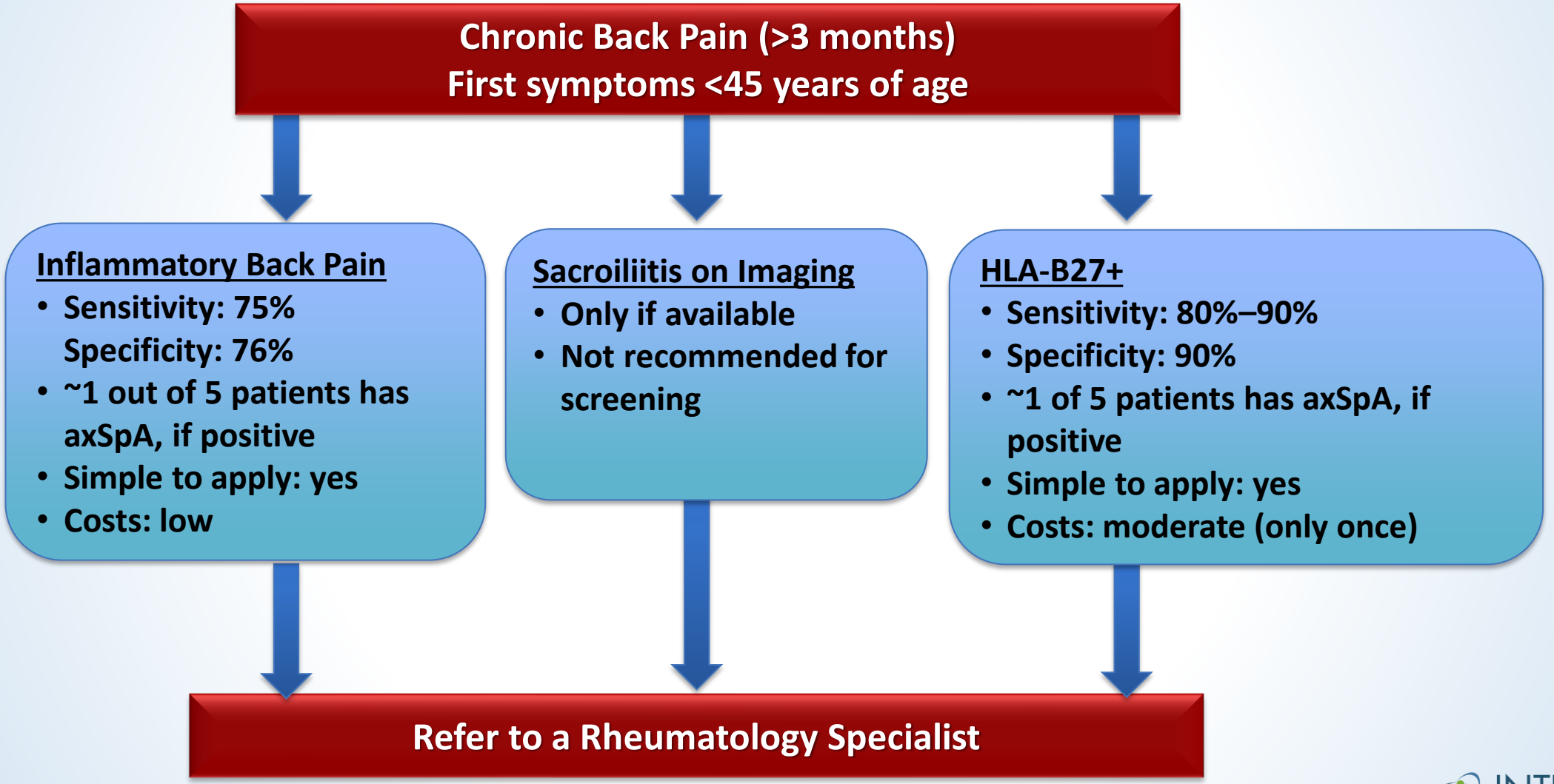
Ward MM, et al. *Arthritis Care Res (Hoboken)*. 2019;71:1285-1299. Images from UpToDate website, 2022.

Factors Contributing to Delay in Diagnosis



Magrey MN, et al. *Mayo Clin Proc*. 2020;95:2499-2508.

Recommendations for Screening and Referral



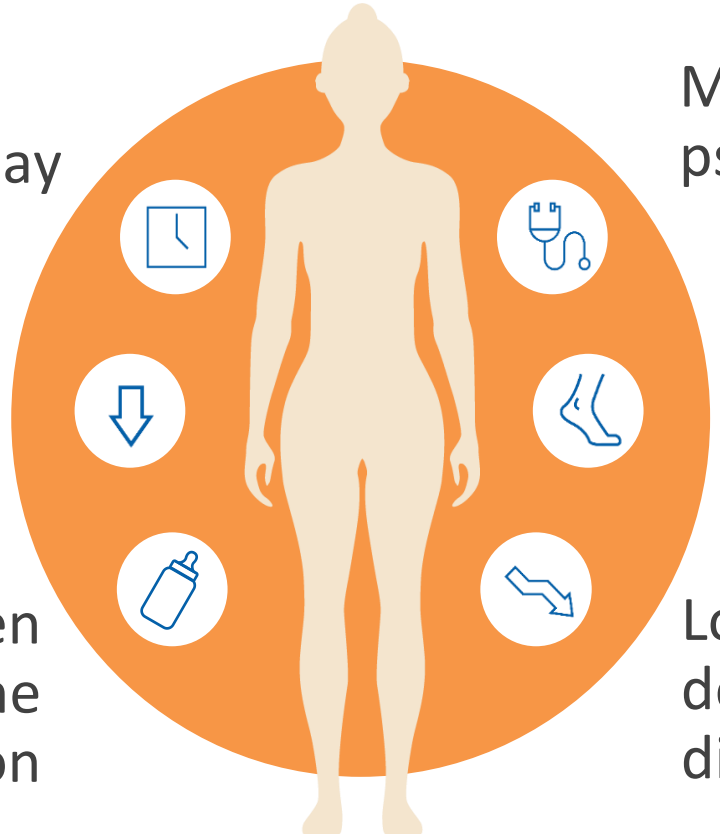
Rudwaleit M, Sieper J. *Nat Rev Rhematol*. 2012;8:262-268.

Women: Different Disease Burden

More diagnosis delay

Poorer quality of life

Less likely to have children than women in the general population



Misdiagnoses of fibromyalgia and psychosomatic disorder

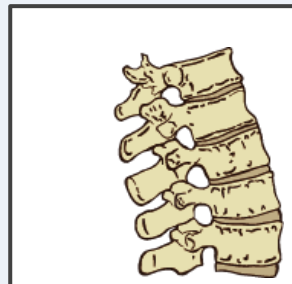
More pronounced enthesitis, disease severity, and peripheral symptoms

Lower inflammatory markers, despite comparable or higher disease severity score

1. Jovani V, et al. *J Rheumatol*. 2017;44:174-183. **2**. Wright GC, et al. *Semin Arthritis Rheum*. 2020;50:687-694. **3**. Webers C, et al. *Rheumatology (Oxford)*. 2016;55:419-428. **4**. Sieper J, et al. *Nat Rev Dis Primers*. 2015;1:15013. **5**. Deminger A, et al. *Arthritis Res Ther*. 2018;20:162. **6**. Mease PJ, et al. *J Rheumatol*. 2021;48:1528-1536. **7**. de Jong HMY, et al. *Scand J Rheumatol*. 2020;49:28-32.

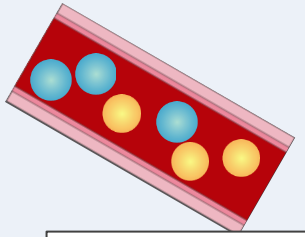
Different Presentations Between Men and Women

Presentation, manifestations, and treatment response different in men and women



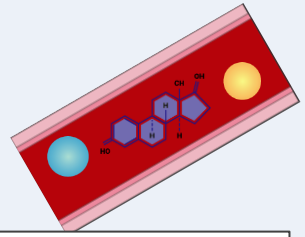
More likely to have syndesmophyte formation

Men

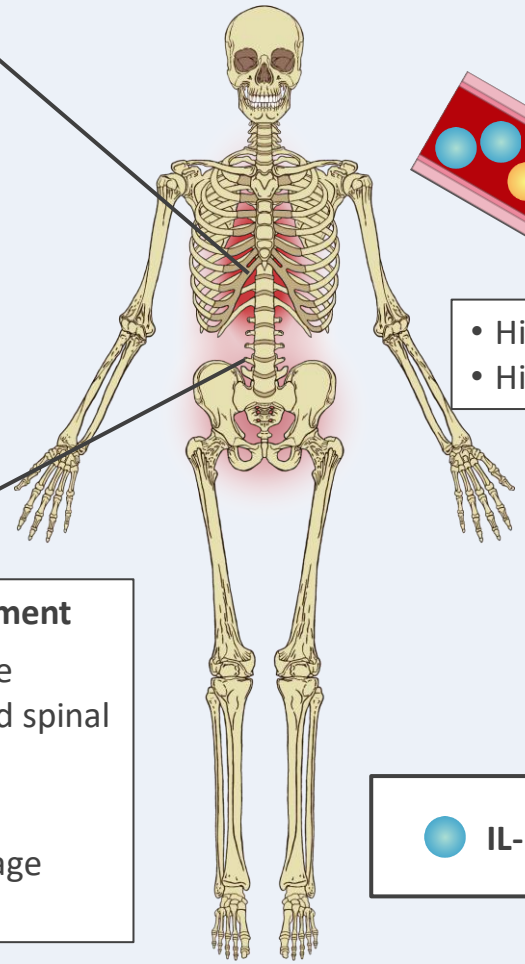


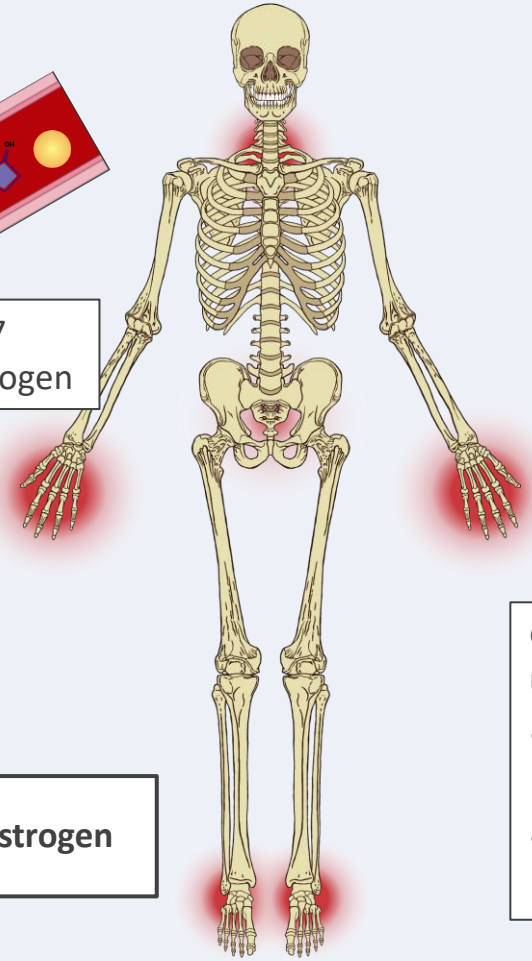
- Higher IL-17
- Higher TNF-α

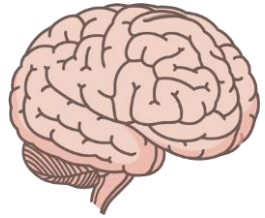
Women



- Lower IL-17
- Higher estrogen





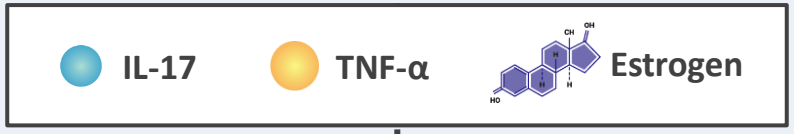


Overall poorer QOL

- Depression & anxiety
- Neuropathic pain
- Fatigue
- Functional impairment

Greater axial involvement

- More likely to have radiographic SI and spinal changes
- Decreased spinal mobility and rib cage flexibility



Greater peripheral and upper axial involvement

- Greater enthesitis/ entheseal tenderness
- Cervical spinal progression

Wright GC, et al. *Semin Arthritis Rheum.* 2020;50:687-694.

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Treatment Assessments, Guidelines, and Therapies

Assessments to Monitor Disease and Treatment Response

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
  - Subjective 6-item questionnaire rating symptoms during the previous week
  - **A score of 4 to 10 indicates active disease**

ASAS20

≥20% improvement *and*

- Absolute improvement of ≥1 unit on a 10-unit scale in at least 3 out of 4 main ASAS domains ***and***
- No worsening by ≥20% and ≥1 unit on a 10-unit scale in the remaining domain

ASAS40

≥40% improvement *and*

- Absolute improvement of ≥2 units on a 10-unit scale in at least three out of four main ASAS domains ***and***
- No worsening in the remaining domain

ASAS5/6

≥20% improvement

in 5 out of 6 ASAS response domains

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BASDAI. Available at: www.basdai.com; Garrett S, et al. *J Rheumatol*. 1994;21:2286-2291; van der Heijde D, et al. *Ann Rheum Dis*. 2017;76:978-991.

Traditional Pharmacologic Treatments

- NSAIDs, including COX-2 inhibitors
  - More effective if prescribed early in disease course
  - In one trial, 35% of patients exhibited a response within 4 weeks
  - Can augment treatment response when added to biologics
- TNF-α inhibitors, a type of bDMARD
  - A meta-analysis of randomized trials with >2,400 patients showed these agents yielded >40% improvement over placebo
- Nonbiologic DMARDs: Methotrexate, sulfasalazine
  - Most appropriate for peripheral SpA
- Corticosteroids
  - 2019 guidelines recommend against use of systemic corticosteroids

bDMARD, biological disease-modifying antirheumatic drug; COX-2, cyclo-oxygenase 2.

Ritchlin C., Adamopoulos IE. *BMJ*. 2021;372:m4447; Baraliakos X, et al. *Rheumatology (Oxford)*. 2017;56:95-102; Callhoff J, et al. *Ann Rhem Dis*. 2015;74:1241-1248; Magrey MN, *Mayo Clin Proc*. 2020;95:2499-2508; Ward MM, et al. *Arthritis Care Res (Hoboken).* 2019;71:1285-1299.

Goals of Treatment

- 3-fold goals
  - Alleviating symptoms
  - Optimizing function
  - Preventing structural damage to the spine
- Early initiation of physical therapy recommended
- Patients who don’t respond to NSAIDs should be referred to a rheumatology specialist
  - To confirm diagnosis
  - Initiate biologic
  - Develop monitoring plan with the patient

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Magrey MN, et al. *Mayo Clin Proc*. 2020;95:2499-2508.

Definitions of Disease Activity and Treatment Response

New in 2019 updates to ACR/SAA/SPARTAN guidelines: Definitions for stable or active disease and nonresponse to treatment — KEY to treatment selection

Term	Definition
Active disease	Disease causing symptoms at an unacceptably bothersome level to the patient and judged by the examining clinician to be due to inflammation
Stable disease	Disease that was asymptomatic or causing symptoms at an acceptable level as reported by the patient; ≥6 months required to qualify as clinically stable
Primary nonresponse	Absence of clinically meaningful improvement in disease activity within 3–6 months after starting treatment; not related to toxicity or poor adherence
Secondary nonresponse	Recurrence of disease activity, not due to treatment interruption or poor adherence after having a sustained clinically meaningful improvement (ie, beyond initial 6 months of treatment)

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Ward MM, et al. *Arthritis Rheumatol*. 2019;71:1599-1613.

Treatments Approved After Publication of 2015 Guidelines

Drug Names*	Approval for AS	Approved for nr-axSpA?	Route	Dosing
IL-17A Inhibitors				
Secukinumab (Cosentyx®)	Jan 15, 2016	Yes, Jun 16, 2020	SC	• **For r-axSpA (AS) and nr-axSpA**[†] – With loading dose: 150 mg at weeks 0, 1, 2, 3, and every 4 weeks thereafter – Without loading dose: 150 mg every 4 weeks
Ixekizumab (Taltz®)	Aug 26, 2019	Yes, Jun 1, 2020	SC	• **For r-axSpA (AS):** 160 mg (two 80 mg injections) at week 0, followed by 80 mg every 4 weeks • **For nr-axSpA:** 80 mg every 4 weeks
JAK Inhibitors				
Tofacitinib (Xeljanz®; XR)	Dec 14, 2021	No	Oral	• **For r-axSpA (AS):** 5 mg 2x/day or 11 mg once daily with XR[‡]
Upadacitinib (Rinvoq®)	Apr 29, 2022	No	Oral	• **For r-axSpA (AS):** 15 mg once daily

*Listed in order of approval date for AS. [†]Dose can be increased to 300 mg every 4 weeks if active AS does not respond. [‡]Dose 5 mg once daily for patients with renal or hepatic impairment. SC, subcutaneous; XR, extended release. Dosing information from package inserts.

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2019 Updates to ACR/SAA/SPARTAN Guidelines for Active Disease

New in 2019 updates to ACR/SAA/SPARTAN guidelines: Recommendations for agents approved since 2015

- Addressed the use of secukinumab, ixekizumab, and tofacitinib
  - Upadacitinib approved in 2022, not mentioned in guidelines
- **1st line:** NSAIDs
- **2nd line:** TNFi conditionally recommended over secukinumab and ixekizumab because of established long-term safety
- **3rd line:** If initial TNFi treatment fails or is contraindicated, secukinumab or ixekizumab should be used over TNFi biosimilar, tofacitinib, sulfasalazine, or methotrexate

TNFi, tumor necrosis factor inhibitor.

Ward MM, et al. *Arthritis Rheumatol*. 2019;71:1599-1613.

TNF-α Inhibitors: 2nd Line After NSAIDs

Generic Name	Trade Name	Route & Dosing
Etanercept	Enbrel	**SC:** 50 mg once weekly or 25 mg twice weekly
Adalimumab	Humira	**SC:** 40 mg every 2 weeks
Certolizumab	Cimzia	**SC:** 400 mg at 0, 2, and 4 weeks → 200 mg every other week ***or*** 400 mg every 4 weeks
Golimumab	Simponi Simponi Aria	**SC:** 50 mg every 4 weeks **IV**: 2 mg/kg at 0 and 4 weeks, then every 8 weeks
Infliximab	Remicade	**IV:** 5 mg/kg at 0, 2, and 6 weeks → 5 mg every 6 to 8 weeks

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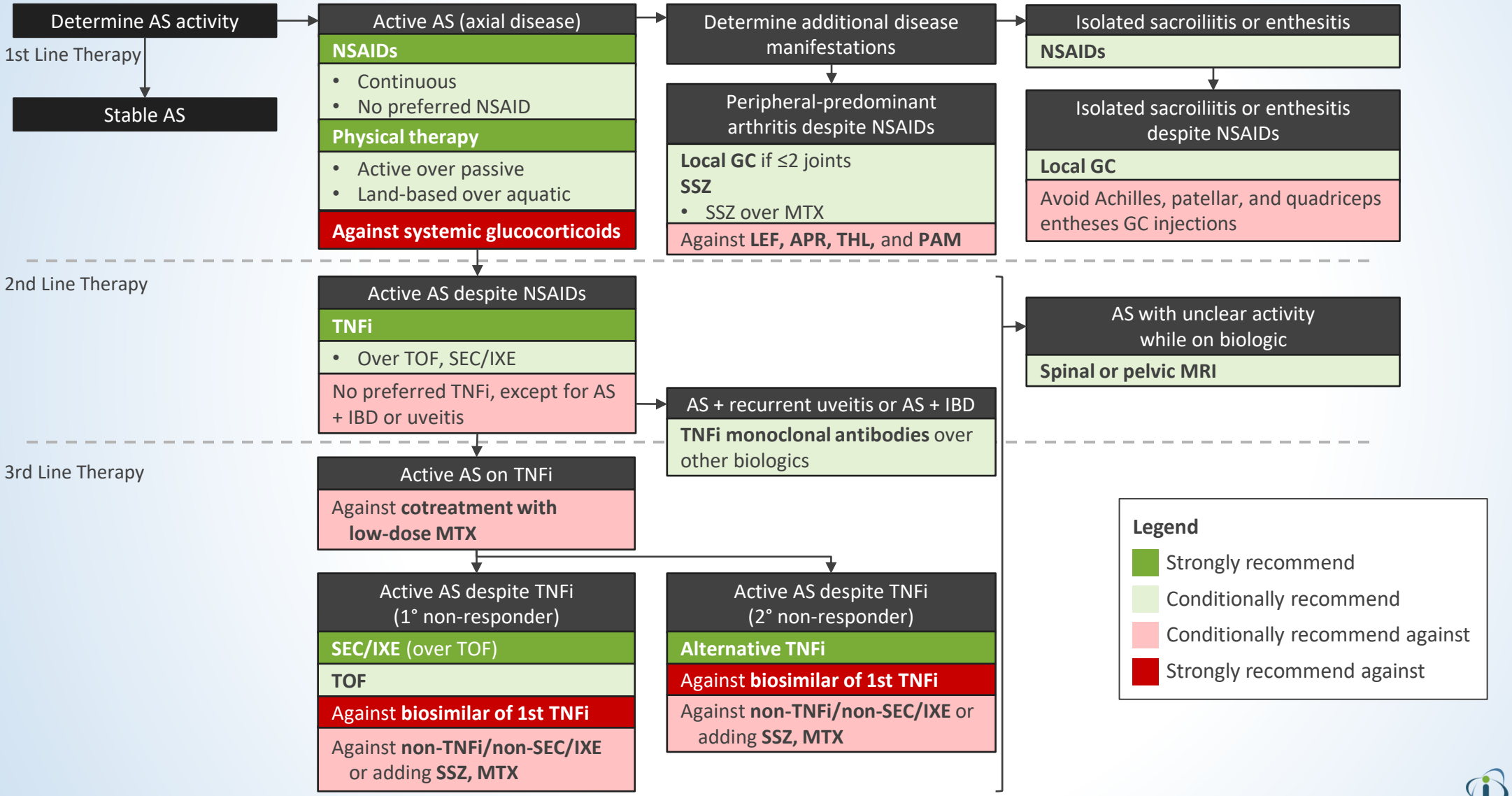
TNF-α Inhibitors

- 45%–57% of AS patients experienced ≥50% disease regression by week 6 or 12, depending on agent
- Durability of response varies; a study of 1,372 AS patients showed most did not stay on the first TNF inhibitor they were started on
  - 40.7% (n=559) discontinued; 26.1% (n=359) switched
  - 67% of males, 77% of female AS patients did not stay on first TNF inhibitor
- Safety: Meta-analysis showed increased risk for infection the most serious risk
  - Screening for latent TB should be done before starting TNF inhibitor

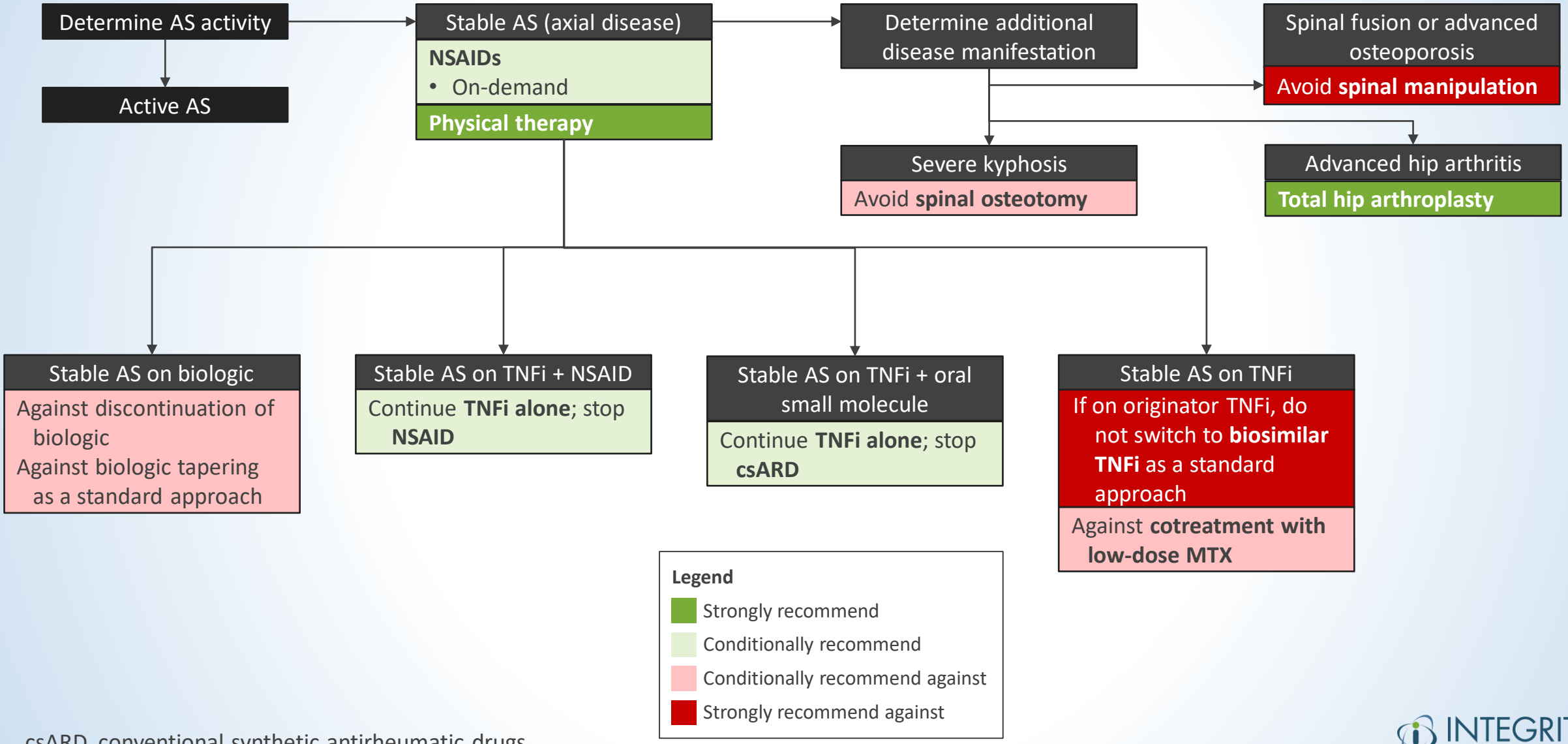
Garcia-Montoya L, Emery P. *Exp Opin Investig Drugs.* 2021;30:1109-1124; Hunter T, et al. *Rheumatol Ther.* 2019;6:207-215; Li J, et al. *Front Pharmacol.* 2021;12:746396.

ACR/SAA/SPARTAN Algorithm for Active Disease



APR, apremilast; GC, glucocorticoid; IBD, inflammatory bowel disease; IXE, ixekixumab; LEF, leflunomide; MTX, methotrexate; PAM, pamidronate; THL, thalidomide; SEC, secukinumab; SSZ, sulfasalazine; TNFi, tumor necrosis factor inhibitor; TOF, tofacitinib. Ward MM, et al. *Arthritis Rheumatol*. 2019;71:1599-1613.

ACR/SAA/SPARTAN Algorithm for Stable Disease



csARD, conventional synthetic antirheumatic drugs.

Ward MM, et al. *Arthritis Rheumatol*. 2019;71:1599-1613.

IL-17A Inhibitor: Secukinumab

- FDA approval for r-axSpA (AS) based on 4 phase 3 clinical trials
  - MEASURE 1: 2-year study with 3-year extension
  - MEASURE 2: 5-year study
  - MEASURE 3: 3-year study
  - MEASURE 4: 2-year study
- FDA approval for nr-axSpA based on 1 phase 3 trial
  - PREVENT: 1-year study

Baeten D, et al. *N Engl J Med.* 2015;373:2534-2548; Pavelka K, et al. *Arthritis Res Ther.* 2017;19:1-10; Kivitz AJ, et al. *Rheumatol Ther.* 2018;5:447-462. Deodhar A, et al. *Arthritis Rheum.* 2021;73:110-120.

Efficacy of Secukinumab for AS in MEASURE Trials

Study	Treatment (mg)	N	ASAS Response Rates (% of Pts)			ASAS Partial Remission
			ASAS20	ASAS40	ASAS5/6	
MEASURE 1	SEC 75	124	60*	33*	45*	16†
	SEC 150	125	61*	42*	49*	15†
	PBO	122	29	13	13	3
MEASURE 2	SEC 75	73	41	26	34	15
	SEC 150	72	61*	36*	43*	14
	PBO	74	28	11	8	4
MEASURE 3	SEC 150	74	58‡	41‡	42‡	10
	SEC 300	76	61†	42‡	40‡	21‡
	PBO	76	37	21	15	1
MEASURE 4	SEC 150 Load	116	60	39	37	--
	SEC 150 No Load	117	62	36	43	
	PBO	117	47	28	29	

*P <.001 vs PBO; †P <.01; ‡P <.05. PBO, placebo; SEC, secukinumab.

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Blair HA. *Drugs.* 2019;79:433-443.

Overall Safety of Secukinumab

Frequency of adverse events of secukinumab across all 4 MEASURE trials

Adverse Events	Frequency
Infections	
Upper respiratory infections	Very frequent
Oral herpes	Frequent
Athlete's foot	Frequent
External otitis	Infrequent
Lower respiratory tract infections	Infrequent
Blood disorder	
Neutropenia	Infrequent
Immune system disorder	
Anaphylactic reactions	Rare

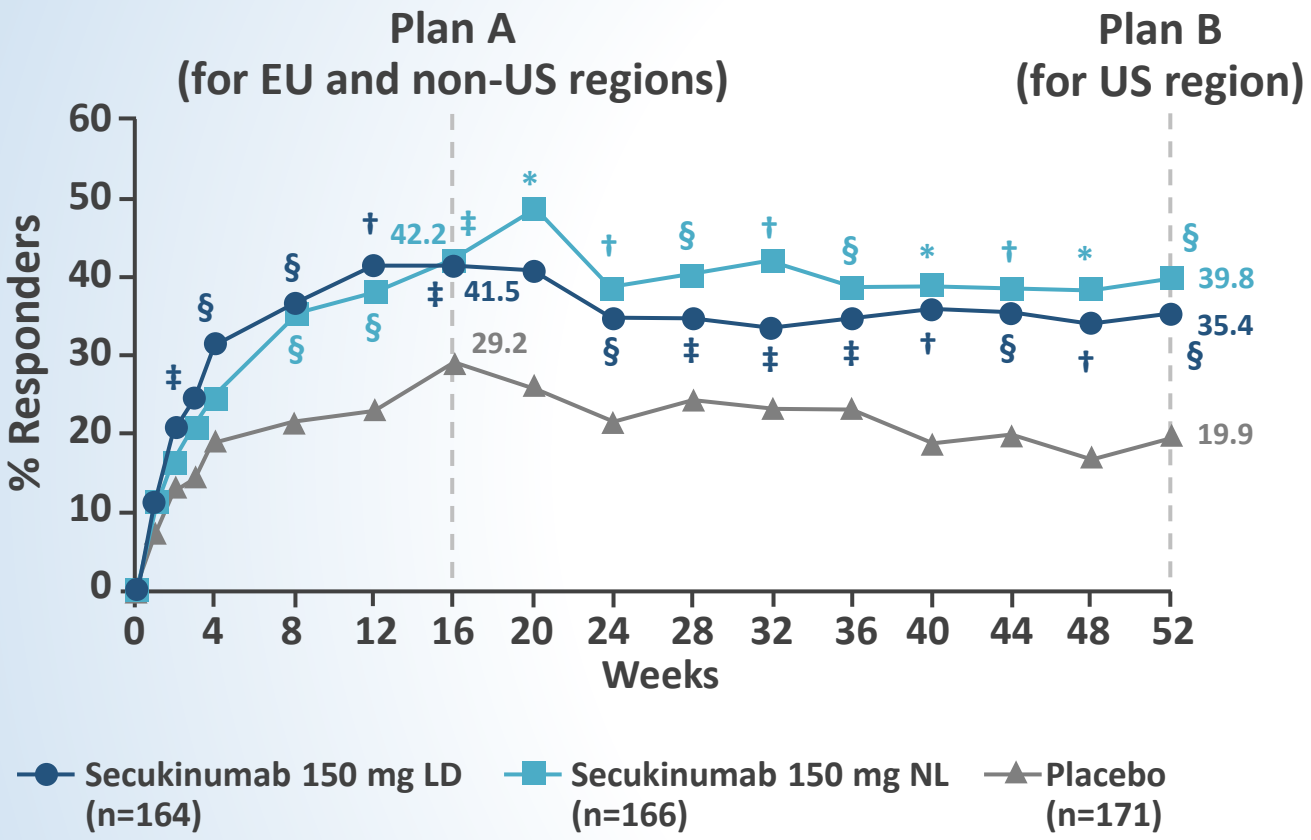
Adverse Events	Frequency
Respiratory disorder	
Rhinorrhea	Frequent
Gastrointestinal disorders	
Diarrhea	Frequent
Inflammatory bowel disease	Infrequent
Skin disorders	
Urticaria	Infrequent
Exfoliative dermatitis	Rare
Ocular disorder	
Conjunctivitis	Infrequent

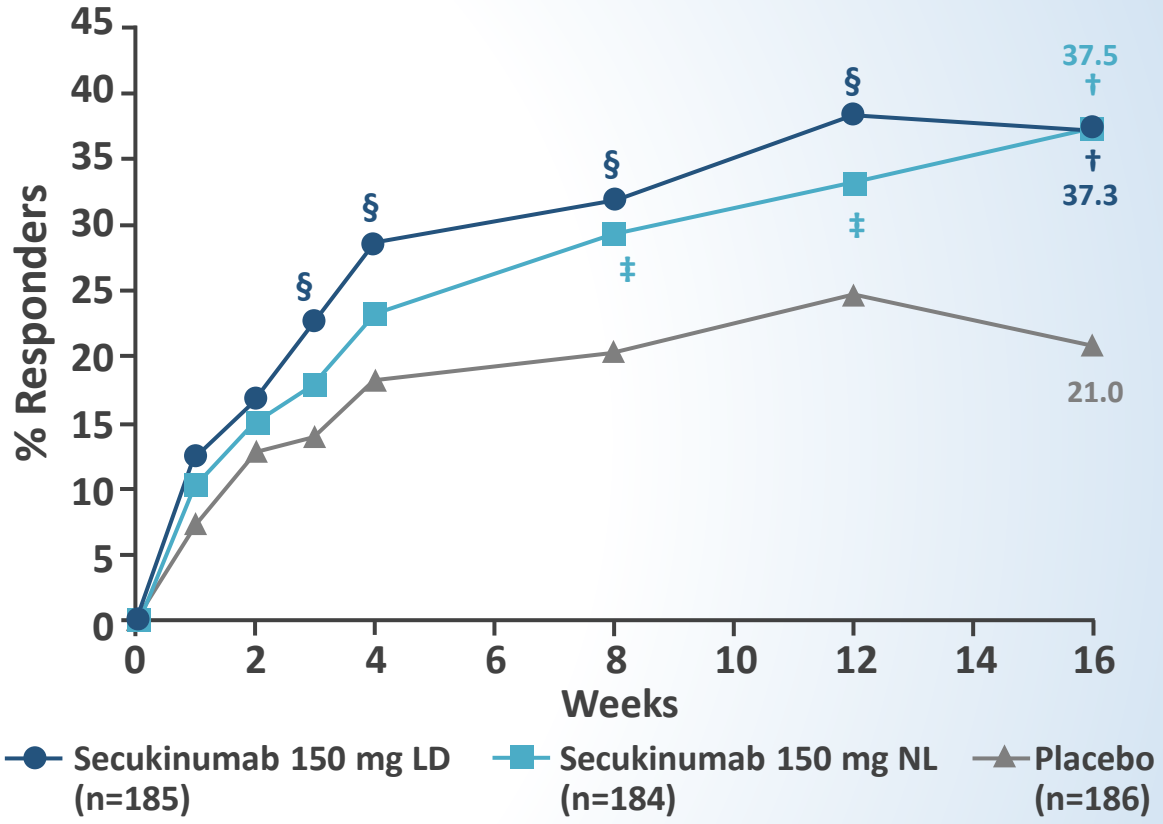
Frequent = ≥ 1/100 to <1/10; Infrequent = ≥1/1,000 to <1/10,000; Rare = ≥1/10,000 to <1/1,000; Very Frequent = ≥1/10.

INTEGRITY CONTINUING EDUCATION

Loricera J, et al. *Exp Opin Drug Safety*. 2021;20:627-634.

Efficacy of Secukinumab for nr-axSpA in PREVENT Trial





Left: ASAS40 response at 16 weeks (analysis plan for European (EU) and non-US) and at 52 weeks (for US analysis).
Right: BASDAI criteria for 50% improvement response in each treatment group through week 16. **P* <.0001; †*P* <.001; ‡*P* <.05; §*P* <.01, vs placebo.

LD, loading dose; NL, non-loading dose.

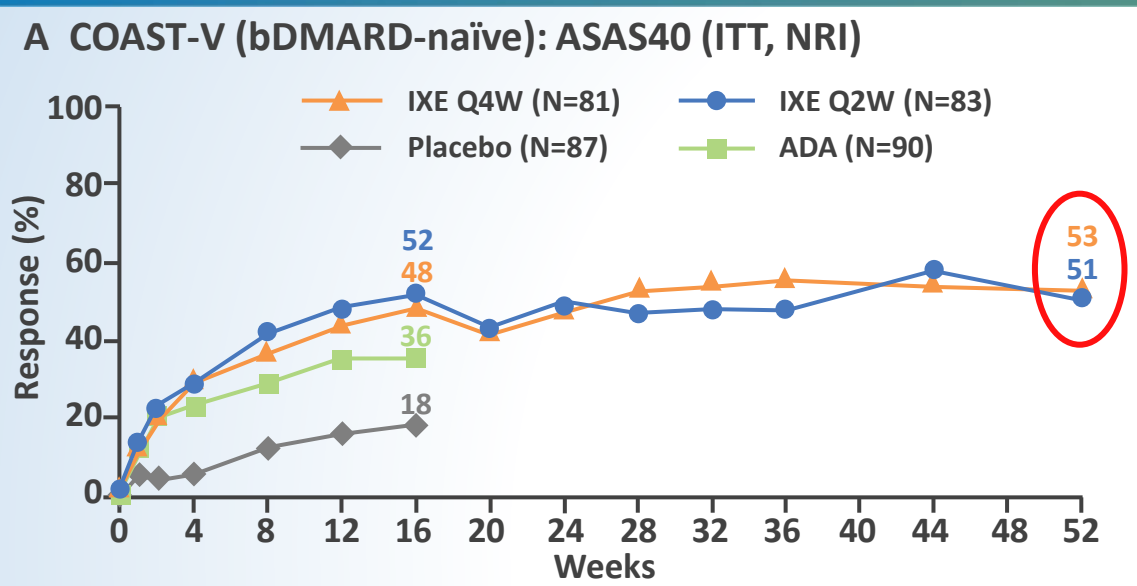
Deodhar A, et al. *Arthritis Rheum.* 2021;73:110-120.

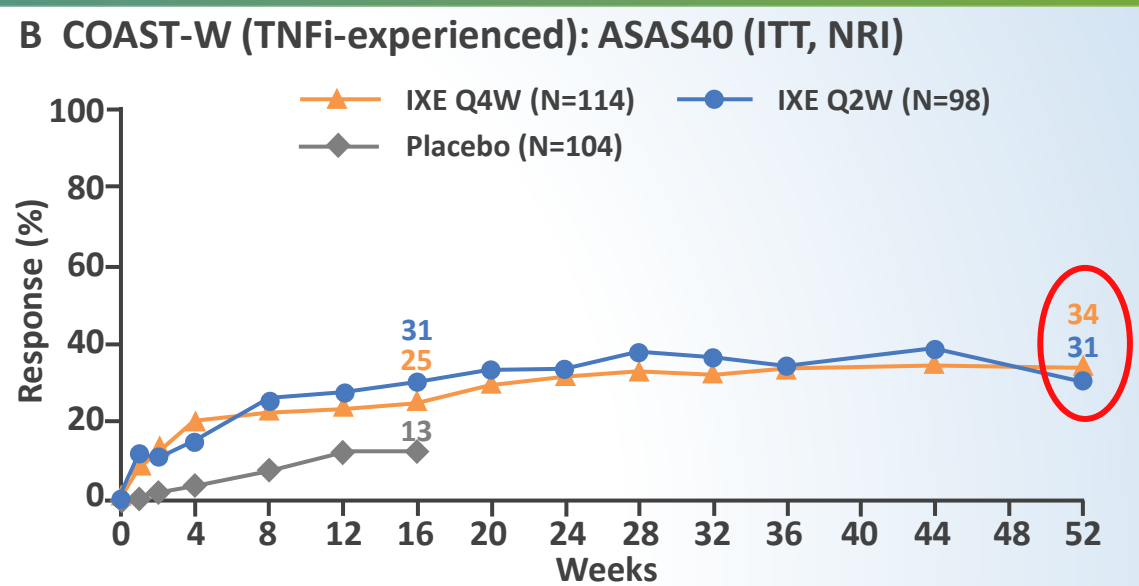
IL-17A Inhibitor: Ixekizumab

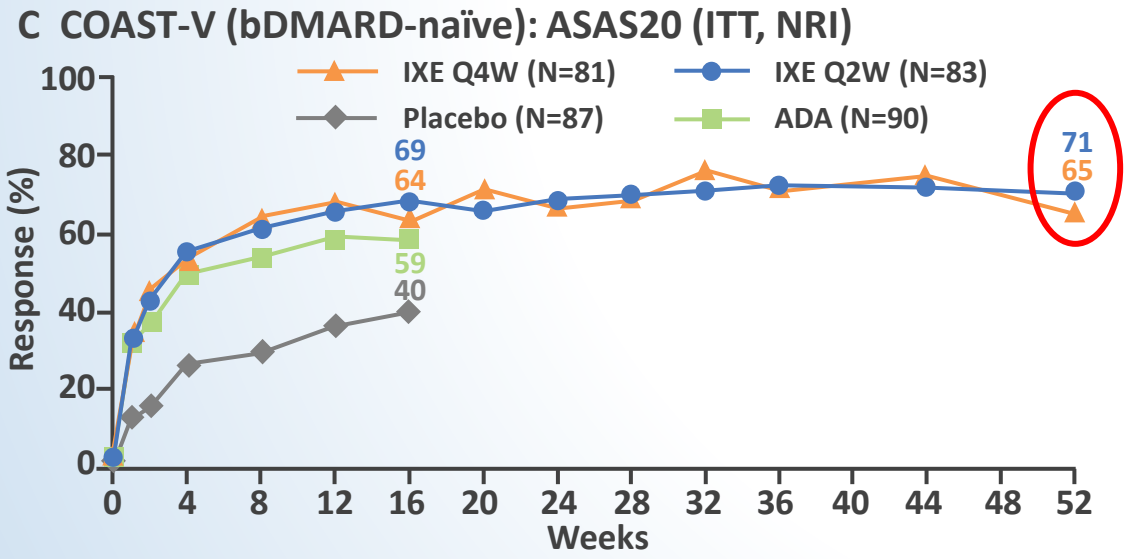
- FDA approval for r-axSpA (AS) based on 2 phase 3 clinical trials
  - COAST-V: bDMARD-naïve patients
  - COAST-W: TNF inhibitor-experienced patients
- FDA approval for nr-axSpA based on 1 phase 3 trial
  - COAST-X: Biologic-naïve patients with active nr-axSpA with objective signs of inflammation

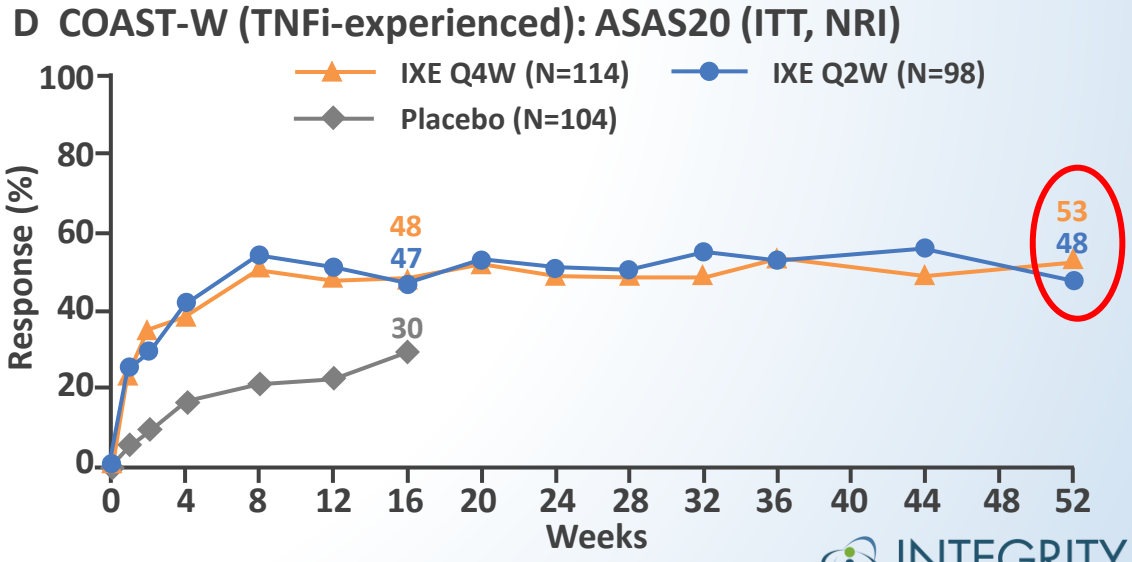
van der Heijde D, et al. *Lancet*. 2018;392:2441-2451. Deodhar A, et al. *Arthritis Rheumatol*. 2019;71:599-611. Deodhar A, et al. *Lancet*. 2020;395:53-64.

Efficacy of Ixekizumab for AS in COAST-V and COAST-W





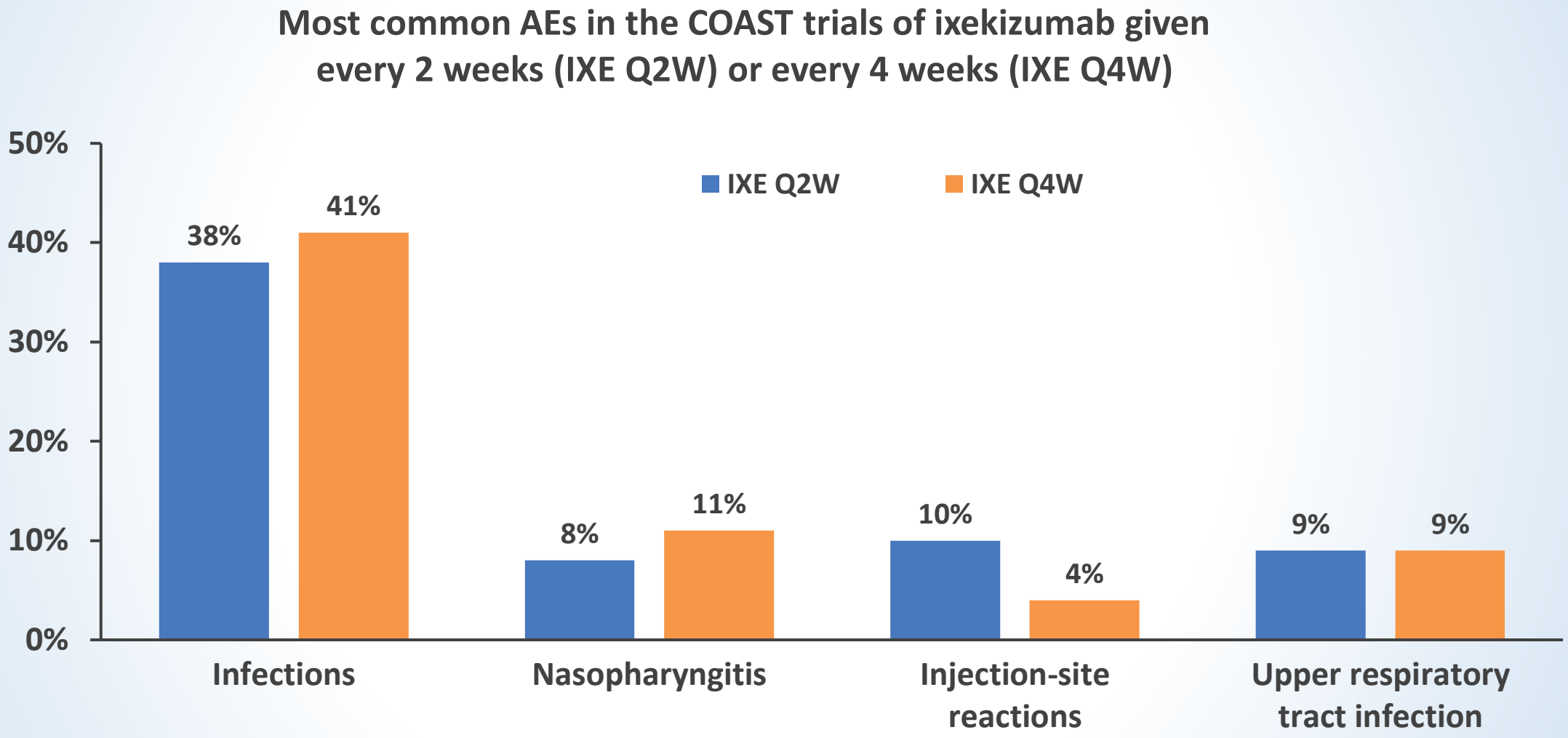




ADA, adalimumab; ITT, intention to treat; NRI, nonresponder imputation; Q2W, every 2 weeks; Q4W, every 4 weeks.

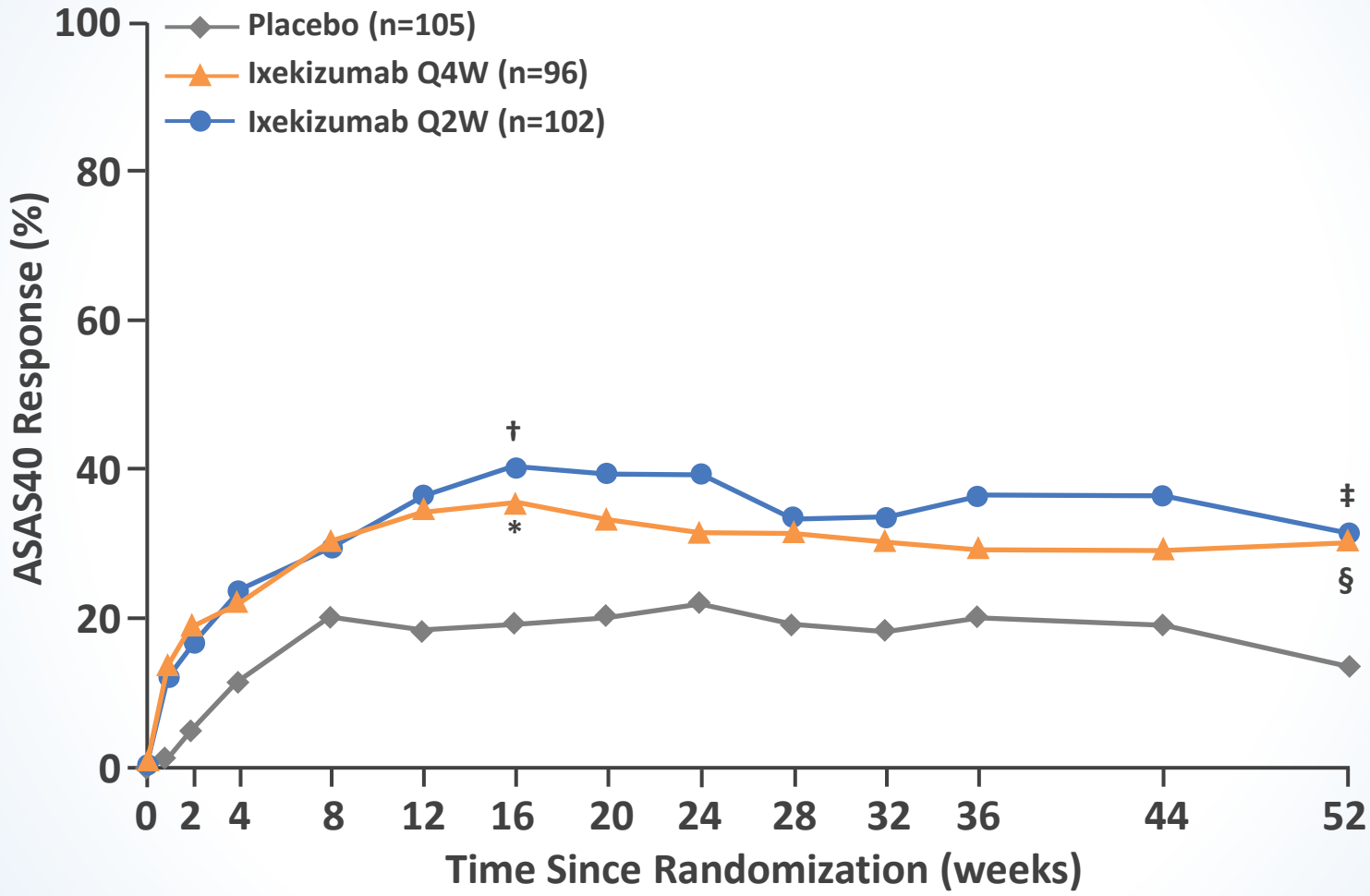
Dougados M, et al. *Ann Rheum Dis*. 2020;79:176-185.

Overall Safety of Ixekizumab



Dougados M, et al. *Ann Rheum Dis*. 2020;79:176-185.

Efficacy of Ixekizumab for nr-axSpA in COAST-X



*P=.0094; †P=.0016; ‡P=.0037; §P=.0045 vs PBO by logistic regression analysis.

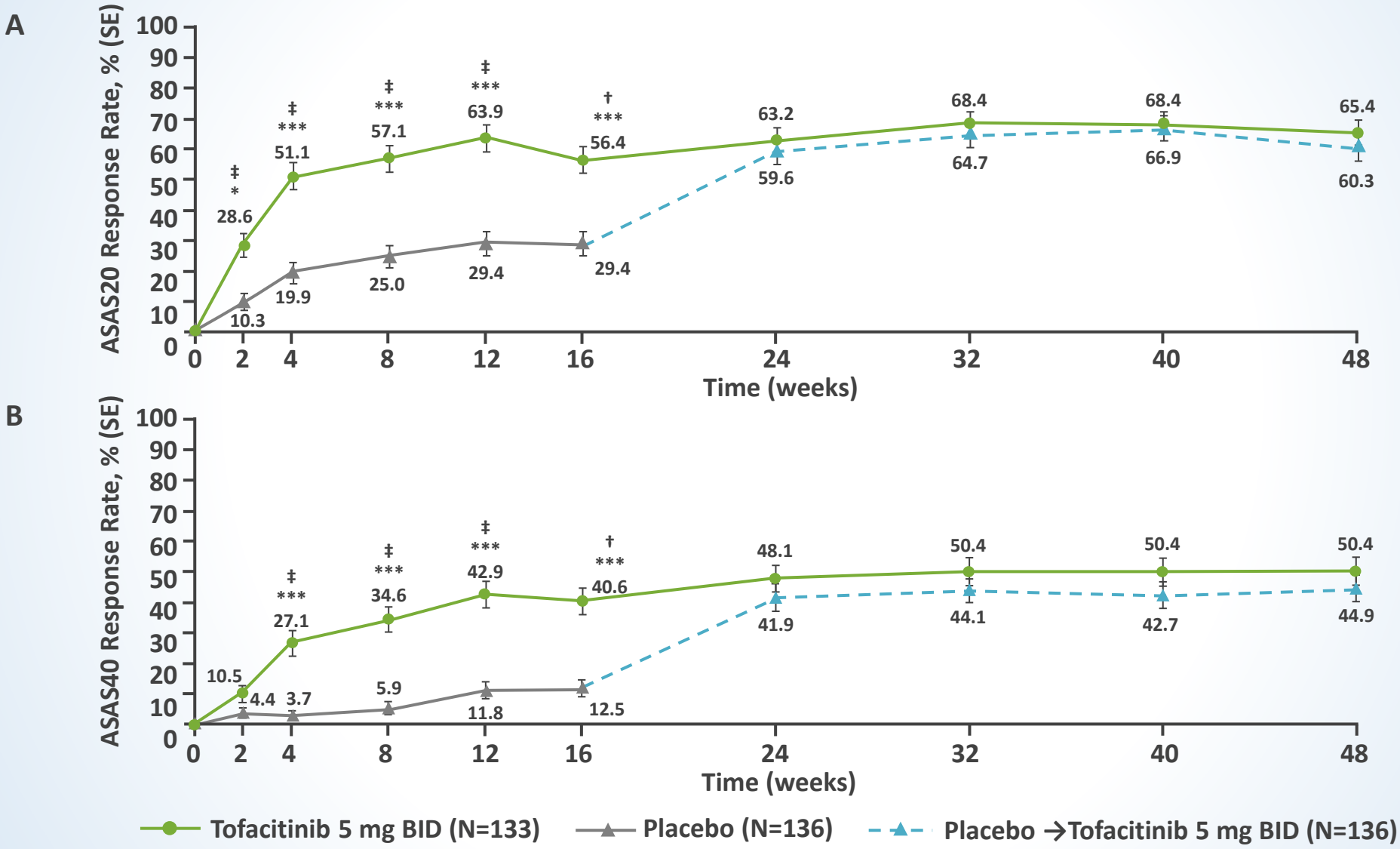
Deodhar A, et al. *Lancet*. 2020;395:53-64.

JAK Inhibitors Approved for AS

- 2 JAK inhibitors now approved for AS patients with inadequate response (or intolerance to) ≥1 TNF-α inhibitor
  - Tofacitinib approved for December 14, 2021 based on phase 3 trial NCT03502616
    - 269 patients with active AS
    - Tofacitinib 5 mg 2x/day vs placebo
  - Upadacitinib approved for April 29, 2022 based on phase 2/3 trial SELECT-AXIS 1
    - 187 patients with active AS
    - Upadacitinib 15 mg once daily vs placebo

Deodhar A, et al. *Ann Rheum Dis.* 2021;80:1004-1013; van der Heijde, et al. *Lancet*. 2019;394:2108-2117.
Deodhar A, et al. *Arthritis Rheumatol.* 2022;74:70-80.

Efficacy of Tofacitinib for r-axSpA in Phase 3 Trial



BID, twice a day. Double-blinded from week 1 to 16; open-label from week 16 to 48.

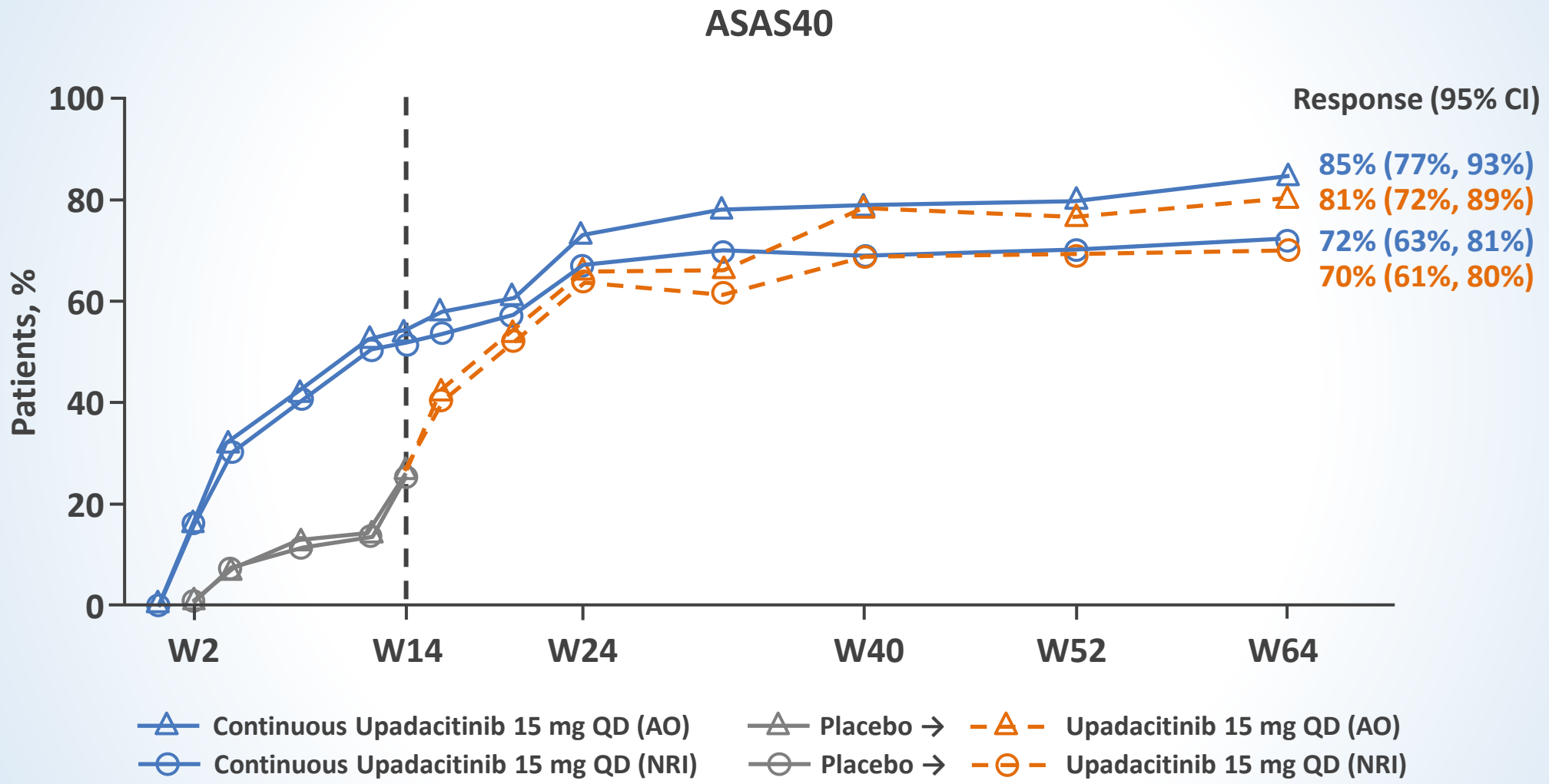
Deodhar A, et al. *Ann Rheum Dis*. 2021;80:1004-1013

Safety of Tofacitinib in Phase 3 Trial for r-axSpA

Patients With Events, n (%)	Up to Week 16 (double-blind phase)		Up to Week 48 (double-blind and open-label phases)	
	Tofacitinib 5 mg two times per day (N=133)	Placebo (N=136)	Tofacitinib 5 mg two times per day (N=133)	Placebo → Tofacitinib 5 mg two times per day (N=136)
AEs	73 (54.9)	70 (51.5)	103 (77.4)	93 (68.4)
SAEs*	2 (1.5)	1 (0.7)	7 (5.3)	2 (1.5)
Severe AEs†	2 (1.5)	0	6 (4.5)	0
Discontinued study drug due to AEs	3 (2.3)	1 (0.7)	8 (6.0)	3 (2.2)
Reduced dose or temporarily discontinued study drug due to AEs	9 (6.8)	5 (3.7)	18 (13.5)	13 (9.6)
Deaths	0	0	0	0
Most common AEs by preferred term (>5% of any treatment group)				
Upper respiratory tract infection	14 (10.5)	10 (7.4)	21 (15.8)	18 (13.2)
Nasopharyngitis	9 (6.8)	10 (7.4)	11 (8.3)	17 (12.5)
Diarrhea	6 (4.5)	5 (3.7)	10 (7.5)	8 (5.9)
Arthralgia	1 (0.8)	8 (5.9)	2 (1.5)	9 (6.6)
ALT increased	4 (3.0)	1 (0.7)	8 (6.0)	2 (1.5)
Protein urine present	5 (3.8)	2 (1.5)	8 (6.0)	4 (2.9)
Headache	2 (1.5)	3 (2.2)	5 (3.8)	7 (5.1)
Abdominal pain upper	0	4 (2.9)	2 (1.5)	7 (5.1)

ALT, alanine transaminase; AE, serious adverse event. Deodhar A, et al. *Ann Rheum Dis*. 2021;80:1004-1013.

Efficacy of Upadacitinib for AS in SELECT-AXIS 1



Double-blinded from week 1 to 14; open-label from week 14 to 64. AO, as observed; NRI, non-responder impumatation.

Deodhar A, et al. *Arthritis Rheumatol*. 2022;74:70-80.

Safety of Upadacitinib in SELECT-AXIS 1

Event	Placebo (n=94)	Upadacitinib 15 mg QD (n=93)
Any AE	52 (55%)	58 (62%)
Serious AE	1 (1%)	1 (1%)
AE leading to discontinuation	3 (3%)	2 (2%)
Infections	26 (28%)	19 (20%)
Increased creatinine phosphokinase	2 (2%)	8 (9%)
Diarrhea	5 (5%)	5 (5%)
Nasopharyngitis	4 (4%)	5 (5%)
Headache	2 (2%)	5 (5%)
Nausea	5 (5%)	1 (1%)

QD, once a day.

van der Heijde, et al. *Lancet*. 2019;394:2108-2117.

Emerging Treatments for axSpA: Phase 3 Trials

Class	Agent	Route	Acronym* / Trial ID	# Pts
IL-17A Inhibitors	Bimekizumab	SC	BE MOBILE 2 / NCT03928743	332
	Netakimab	SC	NCT03447704	228
	Vunakizumab	SC	NCT04840485	529
JAK Inhibitors	Ivarmacitinib	PO	NCT04481139	480
	Upadacitinib	PO	SELECT-AXIS 2 / NCT04169373	734

*If applicable. PO, by mouth.

Source: ClinicalTrials.gov. May 23, 2022, using filters for phase 3, active not recruiting, and recruiting.

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Interactive Patient Case Study

Case Study Introduction

- Justin, age 24, presents complaining of back pain enduring >6 months
- Reports feeling stiff in the morning
- Pain is worse at night
- Works as a PE teacher in junior high school
- Family history: sister has IBD; mother has recurrent uveitis
- Reports that a short course of prednisone did help significantly

Polling Question # 1

Based on this patient's presentation, symptoms, and family history, what would you suspect his diagnosis to be?

A. Back injury/back strain
B. nr-axSpA
C. r-axSpA
D. Uncertain, need additional information

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Polling Question # 2

What tests would you ask for to help confirm a diagnosis for Justin?

A. C-reactive protein
B. HLA-B27
C. Pelvic radiograph (aka, x-ray)
D. MRI

Case Study: Justin, Age 24 (cont)

- A radiograph of Justin's sacroiliac joint shows bilateral sacroiliitis
- Radiograph, symptoms, and family history of uveitis and IBD are conclusive for AS diagnosis

Polling Question # 3

In addition to referring Justin to a rheumatology provider, what would you prescribe?

A. Naproxen 500 mg 2x/day
B. Ibuprofen 800 mg 3x/day
C. Celecoxib 200 mg 2x/day
D. Physical therapy

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Case Study: Justin, Age 24 (cont)

- After 4 weeks of taking the maximum dose of prescribed NSAID, Justin reports minimal response
  - Still experiences back pain
  - Reports that pain is interfering with his job and activities of daily life

Polling Question # 4

Justin's appointment with the rheumatology provider is next week. He asks what you think that provider will prescribe. What will you tell him?

A. TNF-α inhibitor (eg, adalimumab, etanercept)
B. IL-17 inhibitor (ie, secukinumab, ixekizumab)
C. JAK inhibitor (ie, tofacitinib, upadacitinib)
D. Nonbiologic DMARD (eg, methotrexate)

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Program Summary

Program Summary

- 2 main categories in axSpA
  - r-axSpA (also called AS) has radiographic evidence of sacroiliitis
  - nr-axSpA has no radiographic evidence of sacroiliitis
- Chronic, inflammatory back pain the most common symptom
  - Can have non-axial, peripheral and extra-articular manifestations
- No definitive diagnosis test; diagnosis often delayed
- Higher disease burden in women
- Effective biologic and small-molecule drugs now available for r-axSpA and nr-axSpA
  - IL-17A inhibitors: secukinumab, ixekizumab
  - JAK inhibitors: tofacitinib, upadacitinib

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Thank You!