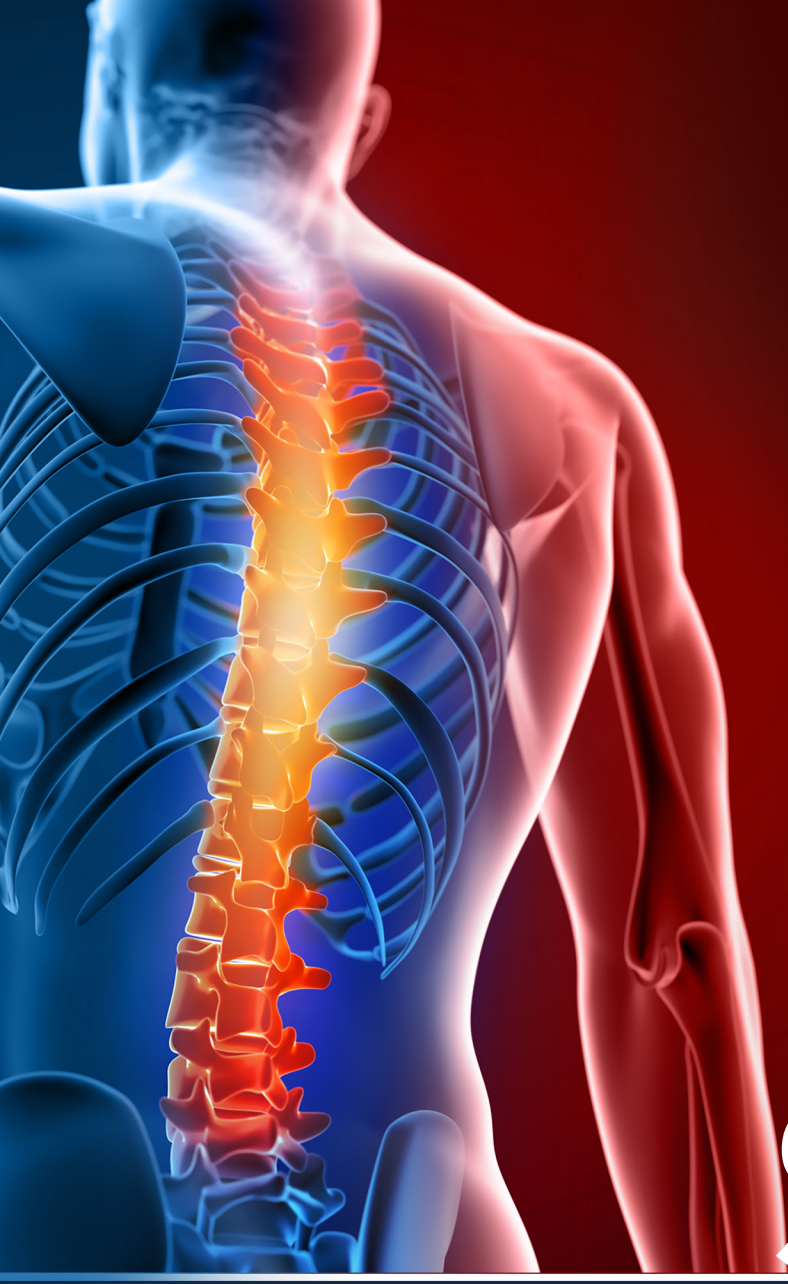

ECHO Series:

Timely Recognition, Management, and Referral of AXIAL SPONDYLOARTHRITIS

Friday, February 26, 2021

FACULTY

Atul Deodhar, MD, MRCP

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by an educational grant from Lilly.

ECHOSeries: Timely Recognition, Management, and Referral of AXIAL SPONDYLOARTHRITIS

AGENDA

Part 1 – Introduction to Axial Spondyloarthritis (AxSpA)

- Spondyloarthritis spectrum
- Disease burden and patient impact
- Pathogenesis of AxSpA

Part 2 – Diagnosis and Initial Treatment Considerations

- Presentation and symptoms
- ASAS classification criteria for AxSpA
- Appropriate use of imaging in AxSpA diagnosis
- Improving physical function, and reducing pain and structural damage

Part 3 – Current and Emerging Treatment Options

- 2019 ACR-SAA-SPARTAN treatment guidelines
- Health and wellness
- NSAIDS
- Clinical trial data on the efficacy and safety of treatment options in nr-AxSpA and AS:
    - TNF-inhibitors (infliximab, etanercept, adalimumab, golimumab and certolizumab pegol)
    - IL-17 inhibitors (secukinumab and ixekizumab)
    - Tofactinib
    - Emerging agents
- Treating-to-target and “window of opportunity”

Part 4 – Case Studies

- Interactive case study presentations with audience participation and discussion

Part 5 – Conclusions and Questions/Answers

ECHO Series: Timely Recognition, Management, and Referral of Axial Spondyloarthritis

FACULTY

Atul A. Deodhar, MD, MRCP, FACR, FACP
Professor of Medicine
Division of Arthritis and Rheumatic Diseases
Medical Director, Rheumatology Clinics, Immunology infusion center, and home infusion program
Oregon Health & Science University
Portland, OR

PROGRAM OVERVIEW

The AxSpA TeleECHO series will explore strategies to promptly recognize, diagnose, and manage patients with axial spondyloarthritis (AxSpA). This TeleECHO series provides an interactive platform that includes didactic programming in addition to case-based discussion on the selection of therapeutic options and the management of patients with AxSpA.

TARGET AUDIENCE

This activity is intended for rheumatologists and other healthcare professionals involved in the management of patients with axial spondyloarthritis.

LEARNING OBJECTIVES

After completing the CME activity, learners should be better able to:

- Identify the disease domains of AxSpA and their relationship to quality of life.
- Assess current and emerging therapies used for AxSpA.
- Examine the IL-17/23 axis and its relationship to the pathophysiology of AxSpA.
- Define sustained remission in patients with AxSpA and implement ways to more effectively pursue it.

ACCREDITATION STATEMENT

Med Learning Group is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
This CME activity was planned and produced in accordance with the ACCME Essentials.

CREDIT DESIGNATION STATEMENT

Med Learning Group designates this live activity for a maximum of 1.0 *AMA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the live activity.

NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in the treatment of patients with Axial Spondyloarthritis. Credits: 1.0 ANCC Contact Hour.

CNE Accreditation Statement: Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

ABIM Maintenance of Certification

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 Medical Knowledge MOC point in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

CONTINUING PHARMACY EDUCATION CREDIT

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

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Pharmacists and Pharmacy Technicians

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NOTE: The only official Statement of Credit is the one you pull from CPE Monitor. You must request your certificate within 30 days of your participation in the activity to meet the deadline for submission to CPE Monitor.

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CME Content Review

The content of this activity was independently peer reviewed.

The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.

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Christina Gallo, SVP, Educational Development for Med Learning Group, has nothing to disclose.

Diana Tommasi, PharmD, Medical Director for Med Learning Group, has nothing to disclose.

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Lisa Crenshaw, Senior Program Manager for Med Learning Group, has nothing to disclose.

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METHOD OF PARTICIPATION

There are no fees for participating and receiving CME credit for this live activity. To receive CME/CNE credit participants must:

1. Read the CME/CNE information and faculty disclosures.
2. Participate in the web-based live activity.
3. Submit the evaluation form to Med Learning Group.

You will receive your certificate upon completion.

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For CME questions, please contact Med Learning Group at info@medlearninggroup.com

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Provided by Med Learning Group

Co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).

This program is co-provided by AMEDCO.

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Timely Recognition, Management, and Referral of Axial Spondyloarthritis

Atul A. Deodhar, MD, MRCP, FACR, FACP

Professor of Medicine
Division of Arthritis and Rheumatic Diseases
Medical Director, Rheumatology Clinics, Immunology infusion center, and home infusion program
Oregon Health & Science University
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1

Disclosures

- Dr. Deodhar discloses that he has received consulting fees and/or research grants from AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly and Company, GlaxoSmithKline, Galápagos, Gilead Sciences, Janssen Pharmaceuticals, Novartis, Pfizer, and UCB.
- During this lecture, Dr. Deodhar may mention the use of medications for both FDA-approved and non-FDA-approved indications.

This activity is supported by an educational grant from Lilly.

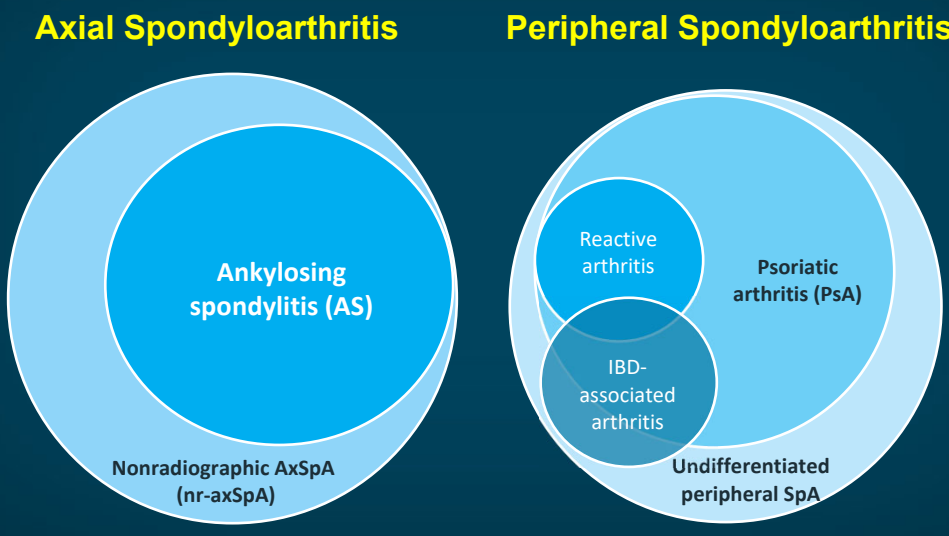
2

Learning Objectives

- Identify the disease domains of axial spondyloarthritis (AxSpA) and their relationship to quality of life
- Assess current and emerging therapies used for AxSpA
- Examine the interlukin (IL)-17/23 axis and its relationship to the pathophysiology of AxSpA
- Define sustained remission in patients with AxSpA and implement ways to more effectively pursue it

3

Spondyloarthritis Spectrum



IBD = inflammatory bowel disease; SpA = spondyloarthritis.
Raychaudhuri SP, Deodhar A. *J Autoimmun*. 2014;48-49:128-133.

4

ASAS Classification Criteria for Axial SpA

In patients with chronic (>3 months) back pain, age at onset <45 years

Sacroiliitis* plus
≥ 1 clinical parameter**

or

HLA-B27+ plus
≥ 2 other clinical parameters**

***Sacroiliitis (x-rays or MRI)**

- Definite **radiographic** sacroiliitis (grade 2 bilaterally or grade 3-4 unilaterally; according to modified New York criteria 1984)

or

- Active (acute) inflammation of sacroiliac joints on **MRI**, highly suggestive of sacroiliitis associated with SpA

****Clinical parameters**

- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's disease/ ulcerative colitis
- Good response to NSAIDs
- Family history for SpA
- Elevated CRP or ESR

ASAS = Assessment of Spondyloarthritis International Society; MRI = magnetic resonance imaging; HLA-B27 = human leukocyte antigen B27; NSAIDs = nonsteroidal antiinflammatory drugs; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

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

5

Natural History of AxSpA Includes nr-axSpA and AS

Garg N et al. *Best Pract Res Clin Rheumatol.* 2014;28(5):663-672.

6

AxSpA Is Associated With Reduced Quality of Life and High Costs

Functional disability[1]
- Correlates significantly with physical function, pain, general health, vitality, and mental health[2]
- Limited physical functioning, including activities of daily living (dressing, walking, bathing, eating), social activities missed, and outside help hired[2,3]

Pain[1]
- Persistent inflammation, chronic back pain, and skeletal changes leading to pain, stiffness, and fatigue[2]
- Contributes to disease burden and physical impairment[2]

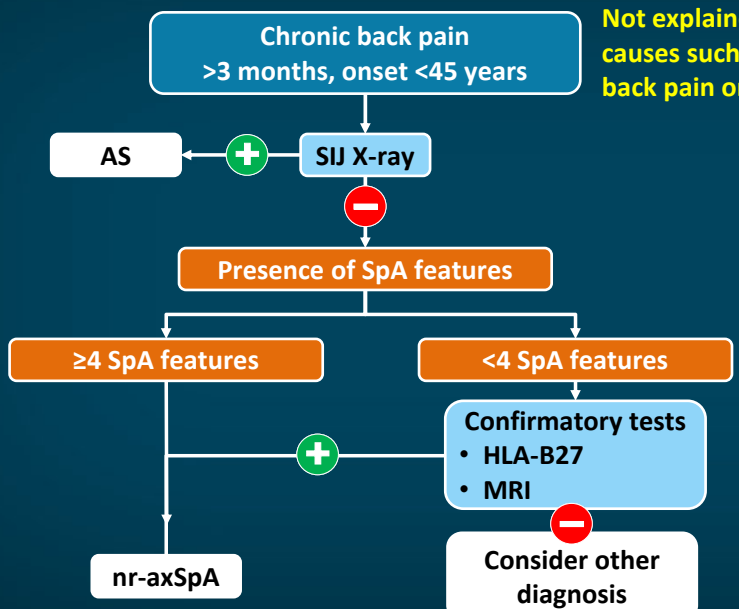
Negative impact on employment and the ability to work[3,4]
- Associated with work instability, changing jobs, and early retirement[2]
- Compounded by typically young age at diagnosis[2]

High costs due to functional disability and disease management[5]

1. Salaffi F, et al. *Health Qual Life Outcomes*. 2009;7:25. 2. Strand V, Singh JA. *J Clin Rheum*. 2017;23:383-389. 3. Osterhaus JT, Purcaru O. *Arthritis Res Ther*. 2014;16:R164. 4. Ward MM, et al. *Arthritis Rheum*. 2008;59:497-503. 5. Ward MM. *Arthritis Rheum*. 2002;46:223-231.

7

How Should We Diagnose AxSpA in Practice?



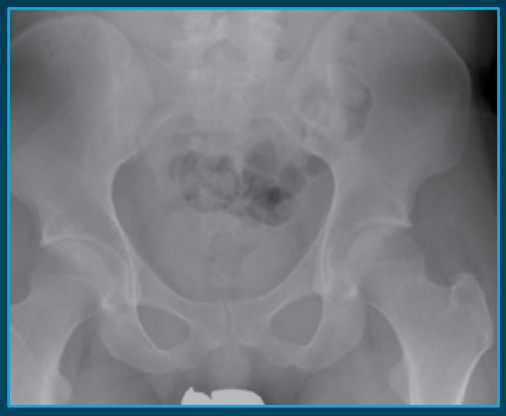
SIJ = sacroiliac joints.

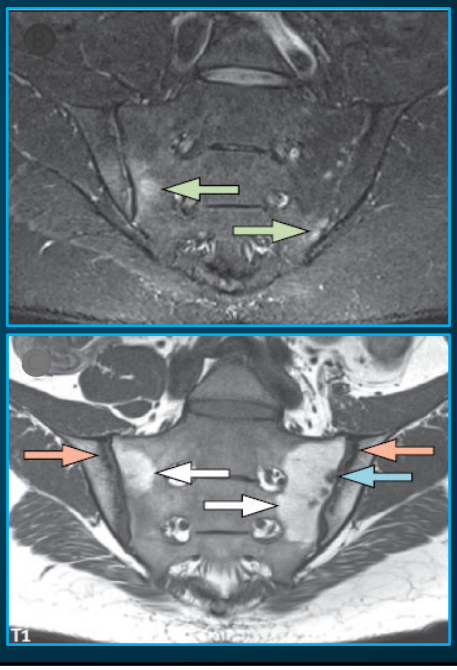
van den Berg R, et al. *Ann Rheum Dis*. 2013;72:1646-1653.

8

Imaging in AxSpA: X-Rays and MRI

- Sacroiliitis on x-rays can be seen in 30% to 50%, with short disease duration (≤ 3 years)
- Limitations: poor reproducibility; interpretation is challenging





- Recommended MRI sequences
  - STIR sequence for detection of active inflammation
  - T1-weighted sequence for detection of postinflammatory changes

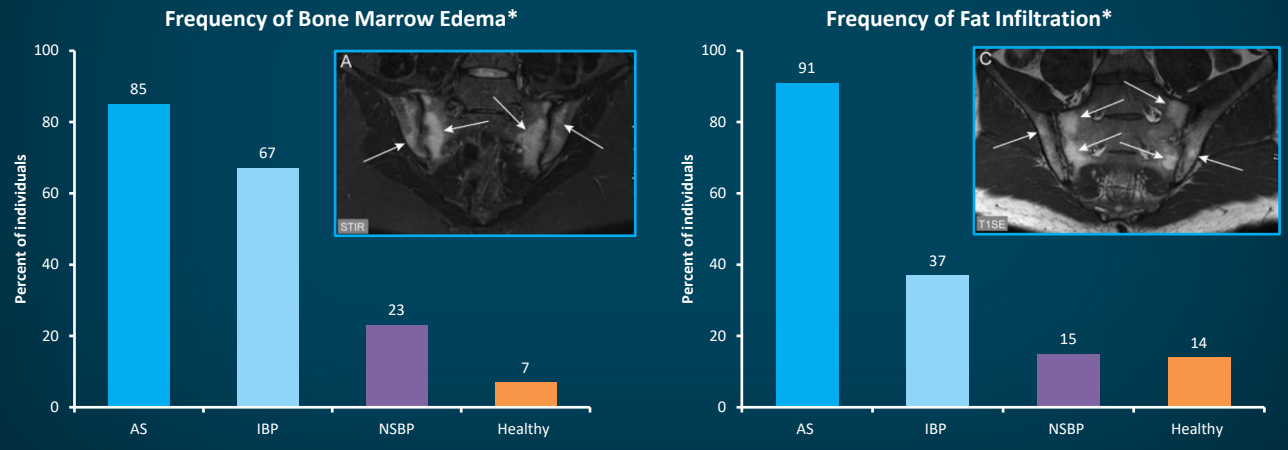
STIR = short tau inversion recovery.

Sieper J, et al. *Lancet*. 2017;390:73-84.

9

Bone Marrow Edema (BME) Occurs in Healthy, Asymptomatic Individuals

Diagnostic utility study of MRI, images from 187 individuals (AS, IBP, NSBP, and healthy)



*Meeting ASAS criteria for positive MRI.

NSBP = nonspecific back pain.

Weber U, et al. *Arthritis Rheumatol.* 2010;62(10):3048-3058.

10

Appropriate Use of Sacroiliac Joint MRI

- Order sacroiliac joint MRI *only if* you have high "pre-test probability" of patient having AxSpA—if the pre-test probability is low, don't order a test!
- Order T1, T2, and STIR images, no contrast required
- Depending only on "bone marrow edema" can lead to overdiagnosis—normal volunteers, degenerative pathology, and athletes can have BME
- Discuss with your radiologist: Does the T1-weighted image also suggest sacroiliitis? Are there any erosions? Any other structural changes? Any fatty changes to suggest old inflammation?

11

How Prevalent Is Axial Spondyloarthritis? NHANES 2009-2010

Mobile examination centers

Centers for Disease Control and Prevention
National Center for Health Statistics

- 5103 of US population surveyed
- 19.2% have chronic back pain (89% currently, 11% in the past)
- 6.9% of the US population has "inflammatory back pain"
- US prevalence of HLA-B27 is 6.1% (Caucasians: 7.5%, Mexican Americans: 4.6%)
- Prevalence of "self-reported provider diagnosed" AS is 0.55%
- Prevalence of AxSpA is 0.9% to 1.4%

Weisman MH, et al. *Ann Rheum Dis*. 2013;72:369-373. Reveille JD, et al. *Arthritis Rheum*. 2012;64(5):1407-1411.

12

Inflammatory Back Pain

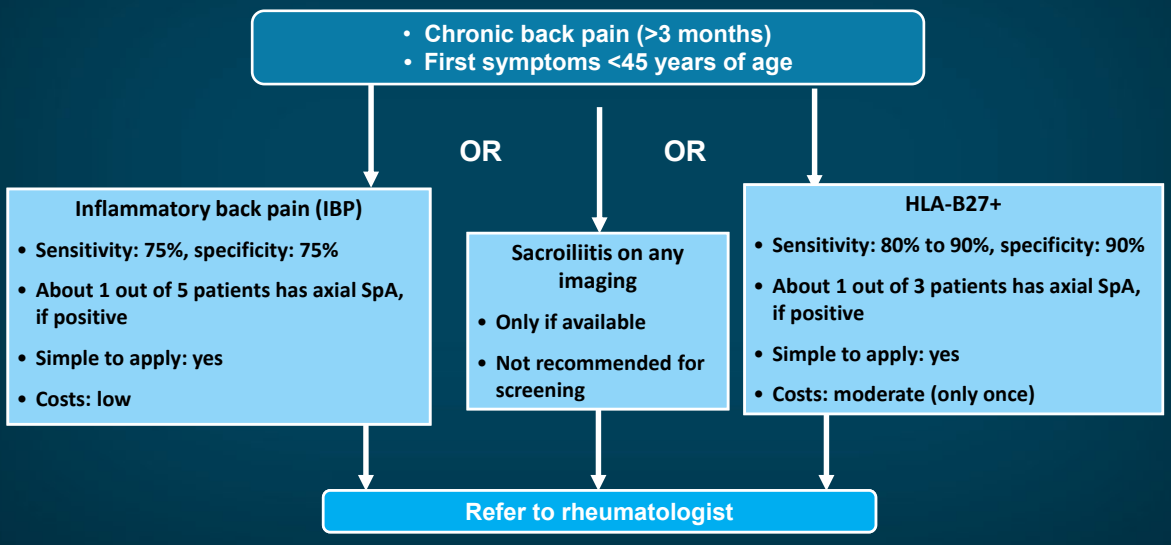
Inflammatory back pain (IBP) according to various criteria

Calin et al[1]	Rudwaleit et al[2]	ASAS[3]
• Age at onset <40 years • Duration of back pain >3 months • Insidious onset • Morning stiffness • Improvement with exercise	• Morning stiffness >30 minutes • Improvement with exercise but not rest • Awakening in second half of night • Alternating buttock pain	• Age at onset <40 years • Insidious onset • Improvement with exercise • No improvement with rest • Pain at night (with improvement upon getting up)
IBP if 4/5 are present	IBP if 2/4 are present	IBP if 4/5 are present

1. Calin A, et al. *JAMA.* 1977;237:2613-2614. 2. Rudwaleit M, et al. *Arthritis Rheum.* 2006;54:569-578. 3. Sieper J ,et al. *Ann Rheum Dis.* 2009;68:784-788.

13

Referral Strategy for Suspected AxSpA in Patients With Chronic Low Back Pain



Sieper J et al. *Ann Rheum Dis.* 2005;64:659-663.

14

Pathogenesis of AxSpA

Genetics

Gut microbiome dysbiosis

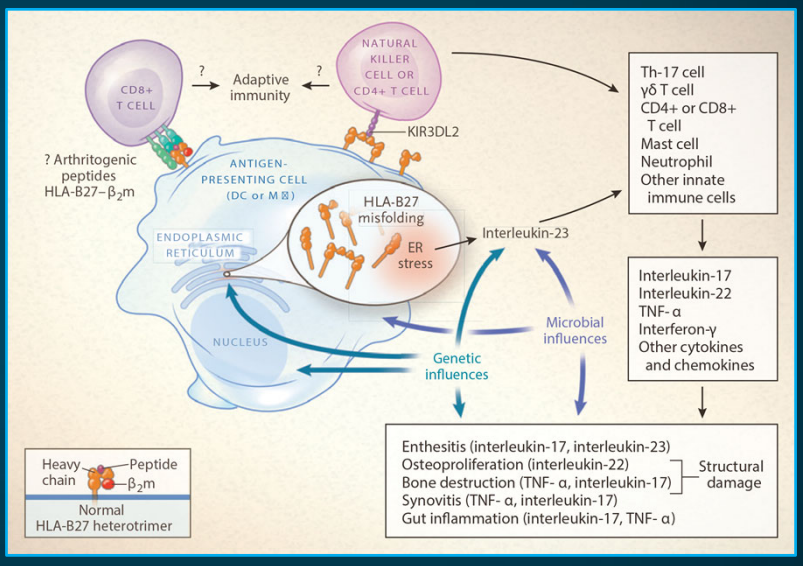
Entheseal trauma and inflammation

Taurog J. et al. *N Engl J Med*. 2016;374(26):2563-2574. Cua DJ, et al. *Nat Med.* 2011;17:1055-1056. Gravallese EM, Schett G. *Nat Rev Rheumatol*. 2018;14(11):631-640.

15

Role of Genetics in AxSpA

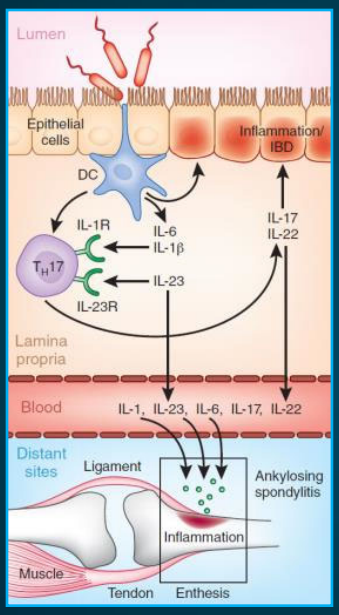
- NK cells or CD4+ T cells recognize dimerized heavy chains of HLA-B27, leading to IL-17 production
- Endoplasmic reticulum stress produced by HLA-B27 misfolding leads to IL-23 production
- IL-23/IL-17 pathway has been implicated in the pathogenesis of AS



Taurog J, et al. *N Engl J Med*. 2016;374(26):2563-2574.

16

Role of Gut Microbial Dysbiosis in AxSpA Pathogenesis

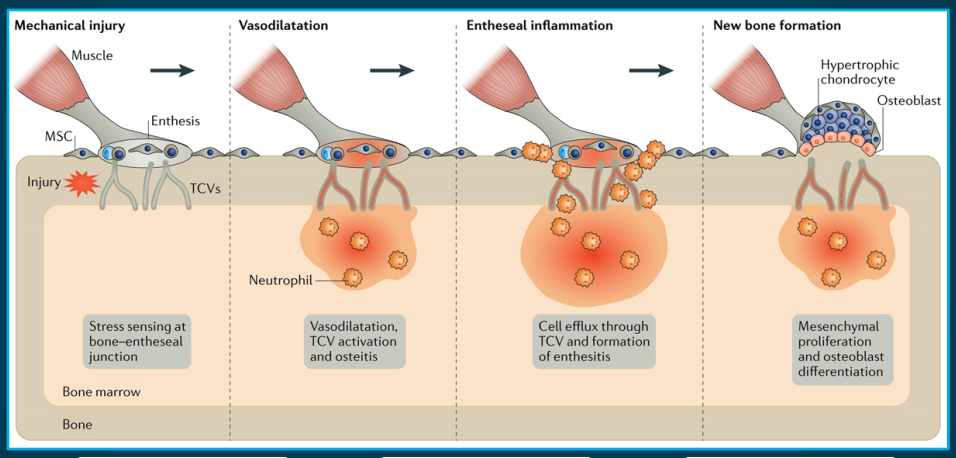


- Gram+ commensal bacteria (eg, SFB) in the gut may play a role in producing inflammatory cytokines (IL-1, IL-6, & IL-23) in mucosa and also a TH17 response, increasing IL-17 and IL-22
- This may initiate IBD but, when overproduced, may spill in systemic circulation, promoting inflammatory diseases in distal sites (ie, joints), perhaps through action upon joint-resident lymphoid cell populations
- Altered sensitivity to IL-23 may predispose people to develop rheumatic diseases, such as AS

SFB = segmented filamentous bacteria.
Cua DJ, et al. *Nat Med.* 2011;17:1055-1056.

17

In a Genetically Primed Host, Mechanical Trauma at Entheses Leads to Innate Immune System Activation and Inflammation



Mechanical Trauma → Neutrophilic Inflammation → "Excessive Repair"

MSC = mesenchymal stem cell; TCV = transcortical microvessels.
Gravallese EM, Schett G. *Nat Rev Rheumatol*. 2018;14(11):631-640.

18

2019 ACR-SAA-SPARTAN Treatment Guidelines for Active AxSpA: First-Line Therapy

Determine AS Activity

First-Line Therapy

Stable AS

Active AS (axial disease)

NSAIDs
- Continuous
- No preferred NSAID

Physical Therapy
- Active over passive
- Land-based over aquatic

Against systemic glucocorticoids

Determine additional disease manifestations

Peripheral-predominant arthritis despite NSAIDs

Local GC if ≤2 joints
SSZ
- SSZ over MTX

Against **LEF, APR, THL,** and **PAM**

Isolated sacroillitis or enthesitis

NSAIDs

Isolated sacroiliitis or enthesitis despite NSAIDs

Local GC

Avoid Achilles, patellar, and quadriceps entheses GC injections

LEGEND
- Strongly recommend
- Conditionally recommend
- Conditionally recommend against
- Strongly recommend against

General Adjunctive Management: unsupervised back exercises, formal group or individual self-management education, fall evaluation/counselling. Monitor using validated AS disease activity measures, and CRP or ESR regularly. Adjunctive management is intended to occur at all stages (from top to bottom of flow figure).

Against using treat-to-target strategy with target of Ankylosing Spondylitis Disease Activity Score (ASDAS) <1.3 or 2.1 over strategy based on provider assessment; against obtaining repeat spine radiographs at a scheduled interval

ACR = American College of Rheumatology; APR = apremilast; GC = glucocorticoid; LEF = leflunomide; MTX = methotrexate; PAM = pamidronate; PICO = population, intervention, comparison, and outcomes; SAA = Spondylitis Association of America; SPARTAN = Spondyloarthritis Research and Treatment Network; SSZ = sulfasalazine; THL = thalidomide.

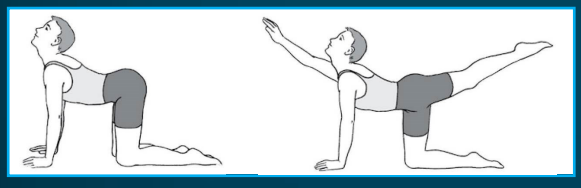
Ward MM, et al. *Arthritis Care Res (Hoboken).* 2019;71:1285-1299.

19

First-Line Therapy in AxSpA

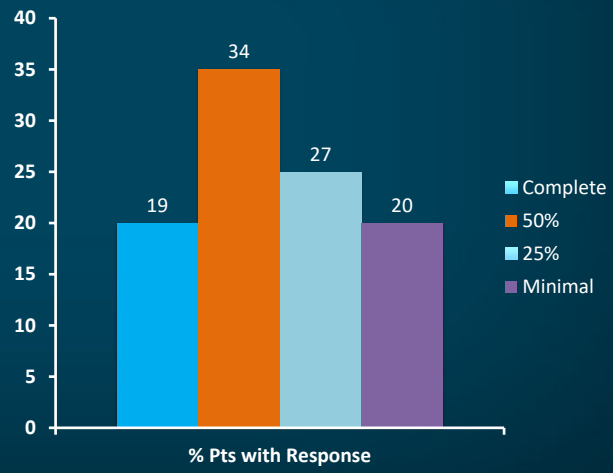
Physical Therapy (PT)

- Meta-analysis of 11 clinical trials on physical therapy found supervised group PT is better than home exercise
- Exercise regimens should be individualized



NSAIDs

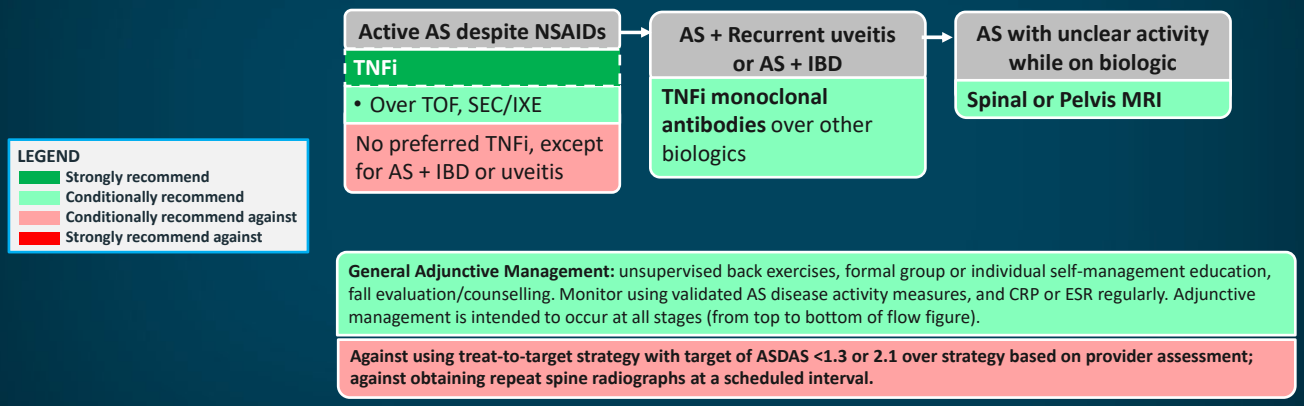
- German cross-sectional study on 1080 patients with AS treated with NSAIDs



Dagfinrud H, et al. *Cochrane Database Syst Rev.* 2008;23(1):CD002822. Zochling J, et al. *Clin Rheumatol.* 2006;25(6):794-800.

20

2019 ACR-SAA-SPARTAN Treatment Guidelines for Active AxSpA: Second-Line Therapy



General Adjunctive Management: unsupervised back exercises, formal group or individual self-management education, fall evaluation/counselling. Monitor using validated AS disease activity measures, and CRP or ESR regularly. Adjunctive management is intended to occur at all stages (from top to bottom of flow figure).

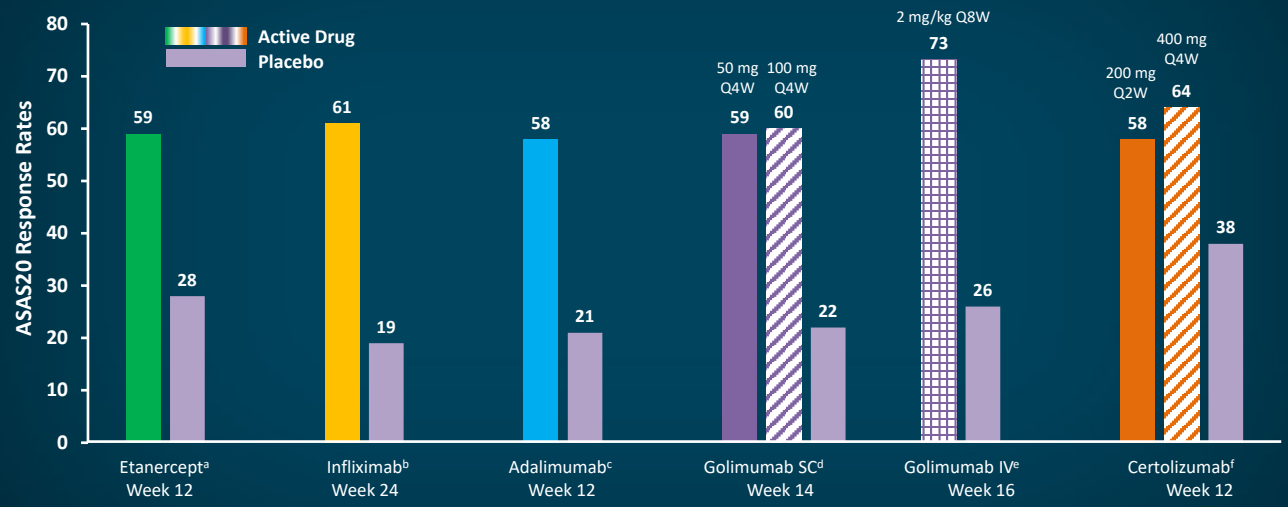
Against using treat-to-target strategy with target of ASDAS <1.3 or 2.1 over strategy based on provider assessment; against obtaining repeat spine radiographs at a scheduled interval.

TNFi = tumor factor necrosis inhibitor; TOF = tofacitnib; SEC = secukinumab; IXE = ixekizumab.
Ward MM, et al. *Arthritis Care Res (Hoboken).* 2019;71:1285-1299.

21

TNF-Inhibitors for Radiographic AxSpA (AS)

Indirect Comparisons of Phase 3 Trials



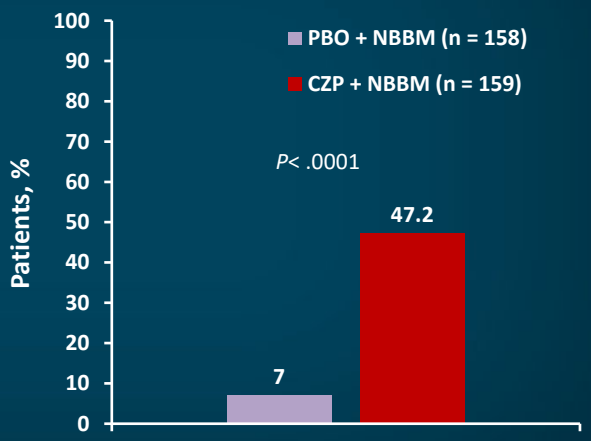
IV = intravenous; SC = subcutaneous; Q4W = every 4 weeks; Q2W = every 2 weeks.
[a]Davis JC Jr, et al. *Arthritis Rheum.* 2003;48:3230-3236; [b]Braun J, et al. *Arthritis Rheum.* 2008;59:1270-1278; [c]van der Heijde D, et al. *Arthritis Rheum.* 2006;54:2136-2146; [d]Inman RD, et al. *Arthritis Rheum.* 2008;58:3402-3412; [e]Deodhar A, et al. *J Rheumatol.* 2018;45:341-348; [f]Landewe R, et al. *Ann Rheum Dis.* 2014;73:39-47.

22

Certolizumab: Phase 3 Study for Patients With nr-axSpA

- Phase 3, 52-week study of 317 patients with active nr-axSpA
- Primary endpoint: ASDAS-major improvement (MI) (% achieving a ≥2.0-point decrease in ASDAS from baseline or achievement of the lowest possible score [0.6] in the ASDAS at Week 52)
- Treatment with certolizumab pegol (CZP)+ nonbiologic background medication (NBBM) resulted in statistically higher proportions of patients achieving ASDAS-MI at week 52 (vs placebo [PBO] + NBBM)

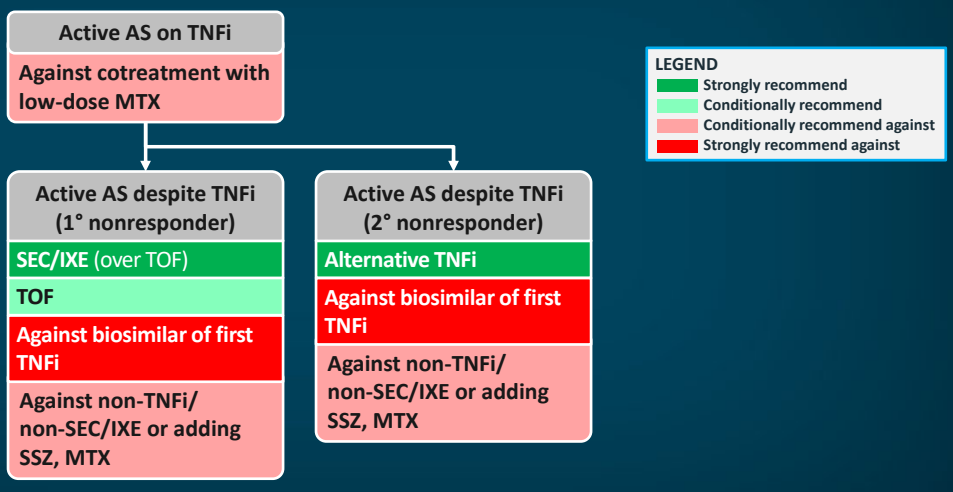
Primary endpoint: ASDAS-MI at Week 52



Deodhar A, et al. *Arthritis Rheumatol.* 2019;71:1101-1111.

23

2019 ACR-SAA-SPARTAN Treatment Guidelines for Active AxSpA: Third-Line Therapy

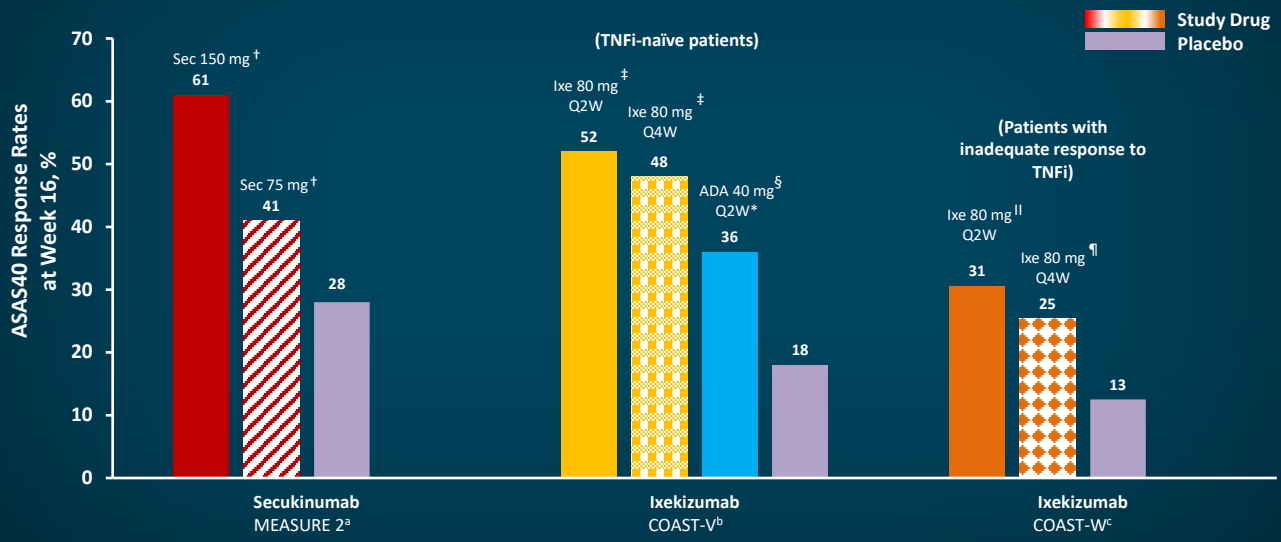


Ward MM, et al. *Arthritis Care Res (Hoboken).* 2019;71:1285-1299.

24

IL-17A Inhibitors in Radiographic AxSpA (AS)

Indirect Comparisons of Phase 3 Trials



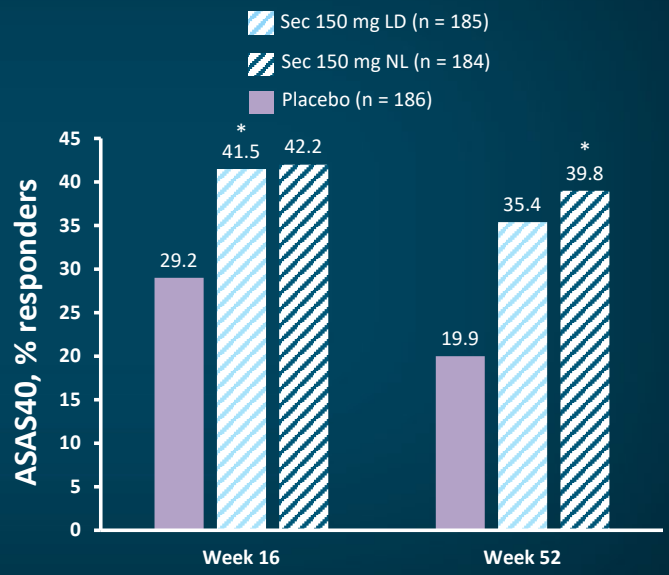
*Active reference group; †P<.001 vs PBO; ‡P<.0001 vs PBO; §P = .0053; ǁP = .003 vs PBO; ¶P = .017 vs PBO; ADA = adalimumab.

[a]Baeten D, et al. *N Engl J Med*. 2015;373:2534-2548; [b]van der Heijde D, et al. *Lancet*. 2018;392:2441-2451; [c]Deodhar A, et al. *Arthritis Rheumatol*. 2019;71:599-611.

25

PREVENT Study: Secukinumab in nr-axSpA

- 555 patients with nr-axSpA
- 2 independent analysis plans per EU (Week 16) and US (Week 52) regulatory requirements
- Primary endpoint: ASAS40 response in TNFi-naïve patients
- No new safety findings were reported



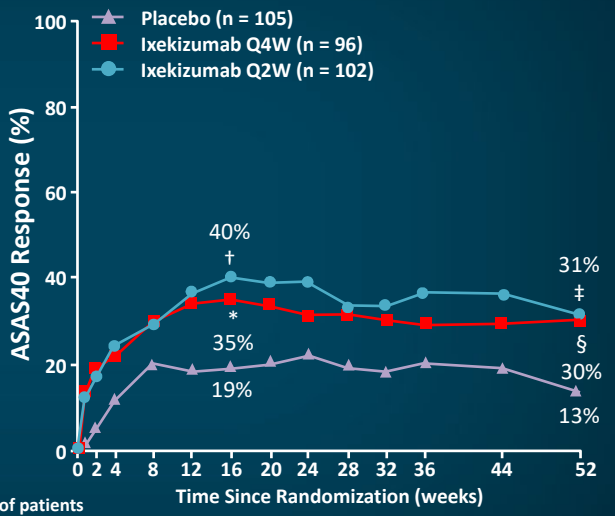
*P <.05 vs PBO. LD = loading dose; NL = nonloading dose.

Deodhar A, et al. *Arthritis Rheumatol.* 2020;73:110-120.

26

COAST-X Trial: Ixekizumab in nr-axSpA

- 303 patients with nr-axSpA who met ASAS classifications (but not New York criteria) and had inflammation either on MRI and/or elevated CRP
- Patients randomized 1:1:1 to 80 mg IXE Q4W, 80 mg IXE Q2W, or PBO; at Week 16, escape to open-label IXE Q2W allowed
- Frequency of serious AEs that led to treatment discontinuation was low and similar across all arms; no new safety signals identified



Number of patients												
Placebo	–	–	–	–	–	99	55	50	43	43	39	36	34
Ixekizumab Q4W	–	–	–	–	–	96	68	64	63	59	56	54	53
Ixekizumab Q2W	–	–	–	–	–	98	73	64	61	60	58	56	52

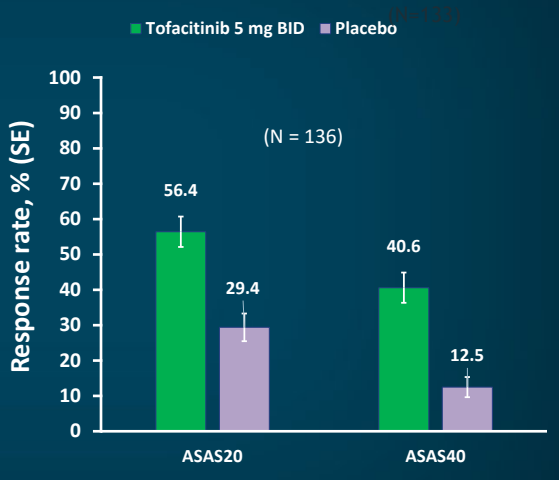
*p = .0094, †p = .0016, ‡p = .0037, and § = .0045 vs placebo.

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

27

Tofacitinib in AS: Phase 3 Trial

- Randomized, double-blind, placebo-controlled trial of tofacitinib 5 mg BID vs placebo to Week 16, then open-label tofacitinib 5 mg BID until Week 48
- Tofacitinib 5 mg BID had significantly higher ASAS20 (1^0 endpoint) and ASAS40 response at Week 16 vs placebo, and also in type-1 error controlled 2^0 endpoints (change from baseline in ASDAS, hsCRP, ASQoL, SF-36-PCS and FACIT-F)
- No VTEs, major adverse cardiovascular events, opportunistic infections until Week 48

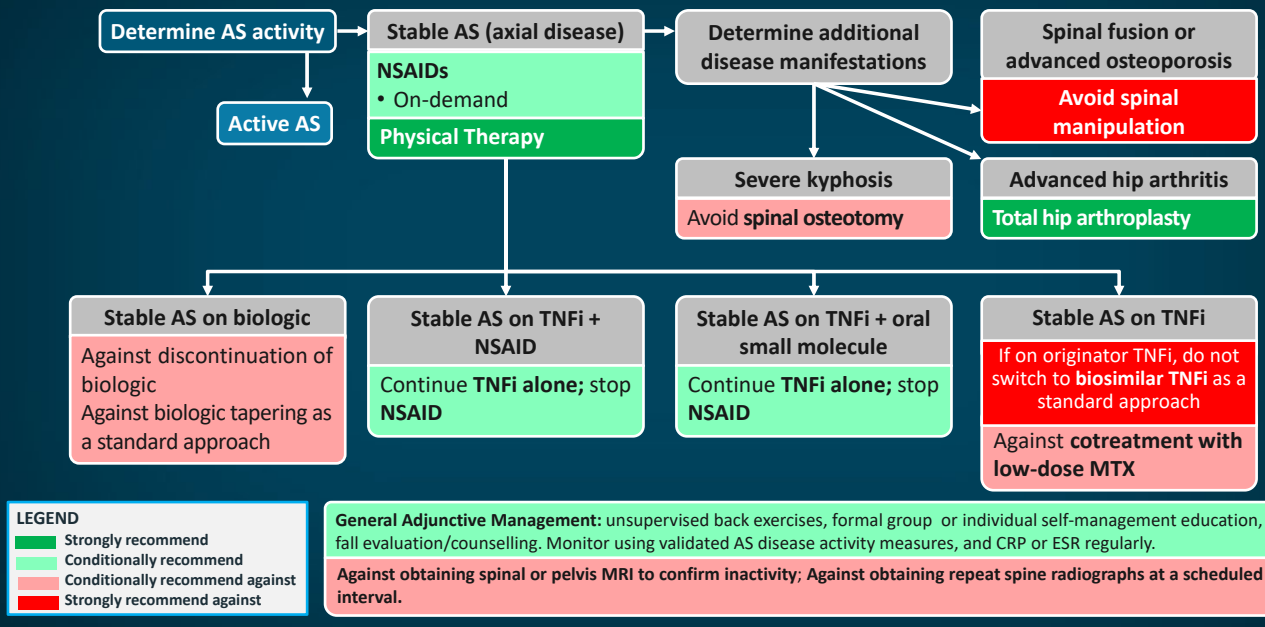


ASQoL = AS Quality of Life; FACIT-F = Functional Assessment of Chronic Illness Therapy – Fatigue; hsCRP = high-sensitivity C-reactive protein; SF-36-PCS = Short Form-36 Health Survey Physical Component Summary; VTE = venous thromboembolism.

Deodhar A. et al. ACR Convergence 2020; Late-Breaking Abstract L11.

28

2019 ACR-SAA-SPARTAN Treatment Guidelines for Stable AxSpA



LEGEND
- Strongly recommend
- Conditionally recommend
- Conditionally recommend against
- Strongly recommend against

General Adjunctive Management: unsupervised back exercises, formal group or individual self-management education, fall evaluation/counselling. Monitor using validated AS disease activity measures, and CRP or ESR regularly.

Against obtaining spinal or pelvis MRI to confirm inactivity; Against obtaining repeat spine radiographs at a scheduled interval.

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

29

Practical Issues Addressed by the 2019 ACR/SAA/SPARTAN Guidelines for AxSpA

- Recommendations for AS and nr-axSpA are similar
- TNFi recommended over SEC/IXE as the first biologic
- SEC/IXE recommended over second TNFi in *primary nonresponse*
- Tofacitinib recommended after TNFi and IL-17i
- Sulfasalazine recommended only for persistent peripheral arthritis
- Spine or pelvis MRI only for unclear disease activity
- *Not recommended*
  - Coadministration of low-dose MTX with TNFi
  - Strict treat-to-target strategy
  - Discontinuation or tapering of biologics *as a standard strategy* in stable disease
  - Routine monitoring with serial spine x-rays

Ward M, et al. *Arthritis Care Res (Hoboken)*. 2019;71:1285-1299.

30

Some Issues With Treat-to-Target in AxSpA

- How many arrows do we have to hit the target?
- Indirect link between ASDAS and modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)—not robust like hemoglobin A1c and cardiovascular mortality
- Should we treat 100% of patients aggressively to benefit 5%? We lack prognostic markers in individual patients
- Can we apply "group level" results to an individual patient?
- The outcome may not be important for the patient
- Personal cost? Societal cost?
- Will treat-to-target do more harm than good (stress, burden, side effects)?
- In Tight COntrol of Psoriatic Arthritis (TICOPA), incremental cost-effective ratio (ICER) of 54,000 pounds (US$70,200) per quality-adjusted life years
- Recent treat-to-target study in axSpA failed to meet primary endpoint

Despite all these issues, early aggressive therapy of AxSpA is recommended by all international guidelines.

31

Tight Control in Spondyloarthritis (TICOSPA): Cluster-Randomized Pragmatic Trial on TC and T2T Strategy in AxSpA

- 1-year, cluster-randomized trial of TC/T2T vs usual care (UC) in 160 patients with AxSpA, bDMARD-naïve, ASDAS >2.1
- **TC/T2T:** Visits Q4W, aiming for ASDAS <2.1, **UC:** Visits Q12W
- **Primary outcome:** >30% improvement in ASAS-Health Index (HI)
- Results: bDMARDs use higher with TC/T2T (56.2%) vs UC (27.2%). *TC not superior despite twice proportion getting bDMARD.*

	1-Year Responses		Cluster and Imbalance-Adjusted Model
	TC/T2T (n = 80)	UC (n = 80)	
ASAS-HI SMD	47.3%	36.1%	NS
ASDAS LDA	76.5%	59.5%	0.03
ASDAS CII	61.2%	46.0%	0.02
ASDAS MI	16.5%	14.9%	NS
ASAS40	52.3%	34.7%	0.01
ASAS20	94.9%	85.9%	0.03
BASDAI 50	79.0%	43.8%	0.03
BASFI (0–10), mean ± SE	1.7 ± 0.5	2.4 ± 0.5	NS

TC = tight control; T2T = treat-to-target; bDMARD = biologic disease-modifying antirheumatic drug.
Molto A, et al. *European League Against Rheumatism (EULAR)* 2020, THU0370.

32

Withdrawal or Dose Reduction of Treatment in Stable AxSpA

RE-EMBARK[a,b]

- 119 patients with nr-axSpA who achieved ASDAS-CRP <1.3 with etanercept 50 mg/wk + NSAIDs withdrew treatment at week 24
- 50% experienced disease flare within 16 weeks vs <25% in EMBARK who continued treatment for 40 weeks
- **24% maintained inactive disease over 40 weeks**

ABILITY-3[c]

- 305 patients with nr-axSpA achieved ASDAS <1.3 at week 28 with adalimumab 40 mg every other week
- Percent of patients **who did not experience a flare** (ASDAS ≥ 2.1) up to and including week 68
  - **70% continuing adalimumab**
  - **47% receiving placebo**

C-OPTIMISE[d,e]

- 313 patients with axSpA who achieved ASDAS <1.3 at week 48 with CZP 200 mg every 2 wk withdrew or reduced dose
- During 48 to 96 week maintenance period
  - **Patient who were flare-free**
    - Full dose: 84%
    - Reduced dose: 79%
    - Placebo: 20%

[a]Van den Bosch F, et al. *Ann Rheum Dis.* 2020;79:70; [b]Maksymowych WP, et al. *Ann Rheum Dis.* 2016;75:1328-1335; [c]Landewé R, et al. *Lancet.* 2018;392:134-144; [d]Landewé RB, et al. *Ann Rheum Dis.* 2020;79:920-928; [e]Landewé R, et al. *Rheumatol Ther.* 2020;7:581-599.

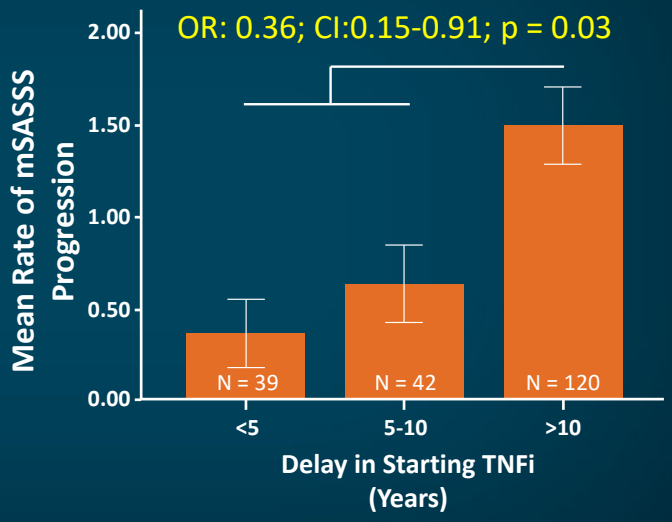
33

Are Biologics "Structure Modifying" in AxSpA?

34

Early Use of TNFi May Reduce Rate of Radiographic Progression

- Prospective Study Of Ankylosing Spondylitis (PSOAS) cohort
- N = 334 with 2 x-rays at least 1.5 years apart (mean = 2.8 years); mean disease duration 16.5 years; 75% male; 83% HLA-B27+
- Baseline ESR, mSASSS, and smoking associated with radiographic progression
- TNFi treatment associated with 50% reduction in the odds of progression (OR 0.52, 95% CI 0.30-0.88, *P* = 0.02)



Haroon N, et al. *Arthritis Rheum.* 2013;65:2645-2654.

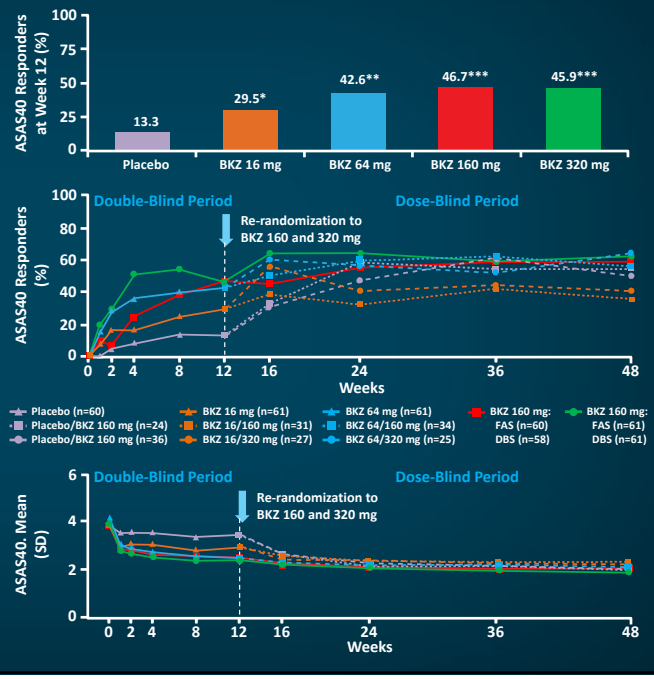
35

What New Options Do We Have on the Horizon to Treat AxSpA?

36

Bimekizumab, an IL-17A and IL-17F inhibitor, in AS

- Both IL-17A and IL-17F are expressed at sites of inflammation and cooperate independently with other cytokines to mediate inflammation
- Randomized, double-blind, placebo-controlled trial of bimekizumab (BKZ) 16 mg, 64 mg, 160 mg, 320 mg, or placebo, Q4W (n = 243)
- **Results**: BKZ was more efficacious than placebo: ASAS20, ASAS40, ASAS-PR, BASDAI50, BASFI
- ASAS40 (nonresponder imputation) at Week 48: 58.6% and 62.3% in patients on BKZ 160 and 320 mg throughout the study; similar ASAS40 responses in rerandomized patients
- Safety profile similar to IL-17i

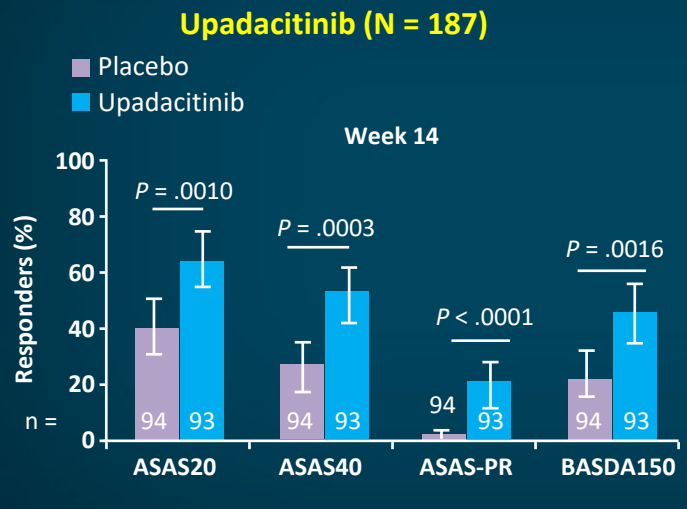


*p <.05, **p<.01, ***p<.001.

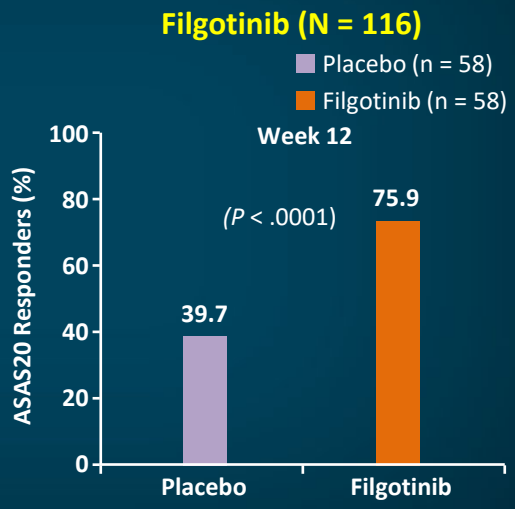
van der Heijde D, et al. *Ann Rheum Dis*. 2020;79(5):595-604.

37

Upadacitinib and Filgotinib (Selective JAK-1 Inhibitors) in AS: Phase 2 Studies



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



van der Heijde D, et a.. *Lancet*. 2018;392:2378-2387.

38

So What Did We Learn Today?

1. Radiographic AxSpA and nr-axSpA are 2 ends of the same spectrum.
2. Prevalence of AxSpA is 1%—patients with AxSpA are missed in primary care providers' offices, chiropractors, and spine centers.
3. Order saroiliac joint MRI *only if* the rest of the clinical picture fits with axSpA—MRI can be false positive in many situations.
4. Treatment guidelines show the way for appropriate management.
5. Aggressive control of inflammation is essential to improve quality of life and prevent radiographic progression, but treat-to-target is not recommended.

39

Case Study

40

Case History

- 39-yr-old white male
- Insidious back pain started age 27
- Alternating buttock pain +
- Better with rest, worse with activity, but would wake him up in the second half of the night
- NSAIDs improved back pain >50% in the past, but not anymore
- No H/O iritis, IBD, psoriasis, enthesitis
- Mother has ankylosing spondylitis

41

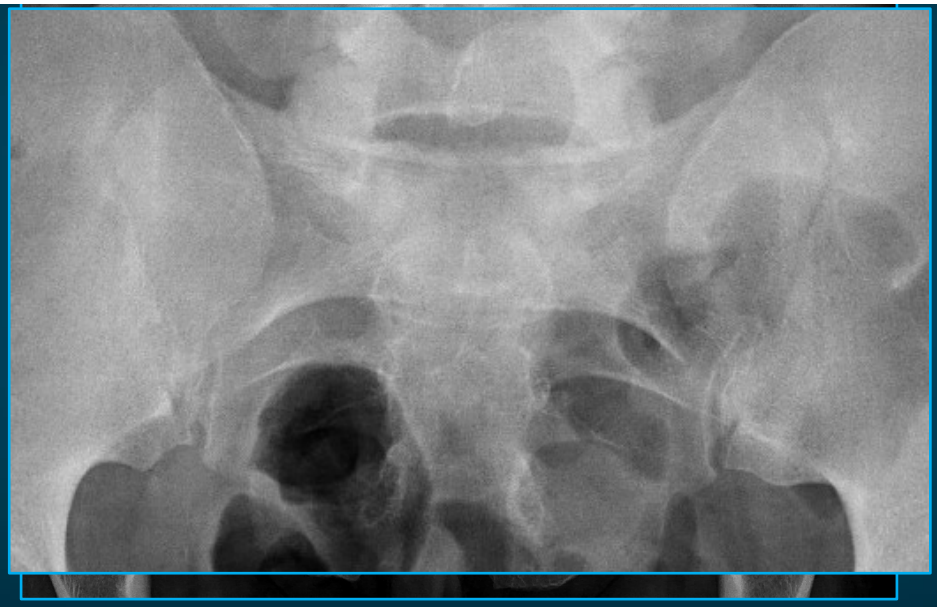
Examination

- O/E
  - Tender on L5, and bilateral PSIS enthesis
  - No synovitis, dactylitis
  - Schober's: 3 cm, occiput to wall: 0 cm, lateral spinal flexion: 22 cm, Tragus to wall: 11.5 cm, chest expansion: 7 cm
- HLA-B27 positive
- CRP <2.9 mg/L
- Back pain 5/10, BASDAI 5.2

42

Imaging

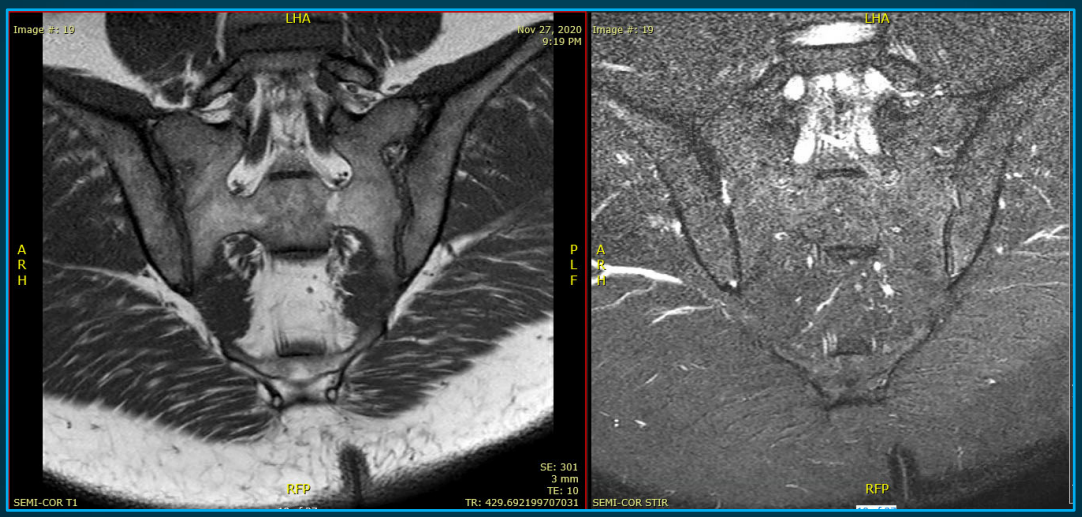
R SI joint is not well profiled, but no erosions, ankylosis or inflammatory sclerosis is seen



43

Additional Imaging

There is mild, bilateral, thin, well-defined, subchondral sclerosis/fibrosis, mostly degenerative. No subchondral edema.



44

How Would You Manage This Patient?

- ***What is the next best step?***

A. This is axSpA – Refer to PT and start full dose NSAID

B. This is axSpA – Start a TNFi

C. This is not axSpA – Refer him to psychiatry

45

Is This AxSpA?

- **Points in favor of axSpA:**
  - Insidious back pain starting before age 45
  - Family H/O axSpA, HLA-B27+ve
  - Alternating buttock pain and past H/O good response to NSAIDs
  - Night time back pain
- **Points against axSpA:**
  - Back pain better with rest, worse with activity
  - No peripheral arthritis, psoriasis, IBD, uveitis
  - No response to NSAIDs
  - No evidence of objective inflammation or structural changes (fat, erosions) on MRI after 12 year history of axial inflammation

46

ASAS Classification Criteria for Axial SpA

In patients with chronic (>3 months) back pain, age at onset <45 years ✓

Sacroiliitis* plus
≥ 1 clinical parameter**

or

✓ **HLA-B27+ plus**
≥ 2 other clinical parameters**

***Sacroiliitis (x-rays or MRI)**

- Definite **radiographic** sacroiliitis (grade 2 bilaterally or grade 3-4 unilaterally; according to modified New York criteria 1984)

or

- Active (acute) inflammation of sacroiliac joints on **MRI**, highly suggestive of sacroiliitis associated with SpA

****Clinical parameters**

- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's disease/ ulcerative colitis
- ✓ Good response to NSAIDs
- ✓ Family history for SpA
- Elevated CRP or ESR

ASAS = Assessment of Spondyloarthritis International Society; MRI = magnetic resonance imaging; HLA-B27 = human leukocyte antigen B27; NSAIDs = nonsteroidal antiinflammatory drugs; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

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

47

Classification Criteria should not be used for diagnosis

'Diagnosis' versus 'Classification'

Diagnostic criteria	Classification criteria
Used by a physician to make a diagnosis	Applied to patients in whom the diagnosis has already been made
When making the diagnosis, the value of diagnostic tests/parameters depends on the prevalence of the disease (pretest probability)	Prevalence of the disease is not important, since all patients should have the disease (have been previously diagnosed)
The purpose of diagnostic criteria/algorithms is to help diagnose individual patients	The purpose of the classification criteria is to provide a unique language for researchers to evaluate homogenous groups of patients, which facilitates comparisons of clinical or experimental studies
Criteria for diagnosis should have a high sensitivity in order to identify as many patients with the disease as possible	Criteria for classification should have a high specificity (close to 100%) in order to avoid misclassification (inclusion of patients who do not have the disease)
Should allow for flexibility in diagnostic confidence (definite, probable, possible)	Gives a yes or no answer (criteria fulfilled or not fulfilled)
Applies to the individual patient	Applies to groups of patients

Deodhar A. *Clin Rheumatol*. 2014;33(6):741–47.

48

Can someone have axSpA with a completely normal MRI?

49

Can someone have axSpA with completely normal MRI?

- Can someone have SLE with negative MRI?
- Can someone have PMR with normal ESR and CRP?

- Yes. The 'gold standard' is always rheumatologist's diagnosis
- However, consider the following in cases where we have to make such a diagnosis
  - What other 'objective' findings do we have (IBP is *not* objective!)
  - How long does the patient have symptoms? Longer durations (>2 years) should have some objective changes on MRI (inflammation on STIR, fat, erosions, sclerosis on T1)
  - Beware of "trial of a biologic": what if the patient returns and reports 20% benefit? Is that enough evidence for a diagnosis?
  - Your word, your opinion, carries a lot of weight

50

Case Study

51

Case History

- 27-yr-old Russian male
- While in Russia, developed iridocyclitis at age 14
- Admitted to hospital for ‘steroid eye injections’, found to be HLA-B27+
- R buttock pain at age 18 while playing soccer, no specific trauma
- Initially activity made it worse, later more training made it better
- Nimesulide (NSAID) made pain better by >50%
- No H/O psoriasis, IBD, and no family H/O spondyloarthritis
- Moved to the US at age 21, seen in NYC by a rheumatologist & diagnosed with AS
- Started on Etanercept

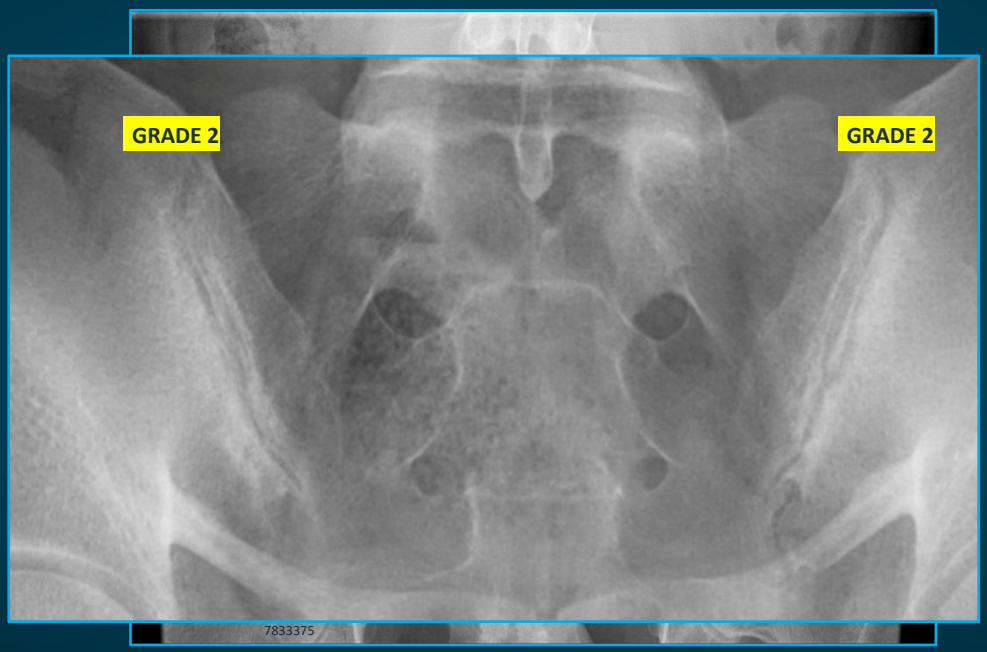
52

Examination

- Moved to Oregon a year ago
- Off etanercept for 6 months
- No more attacks of iritis, currently not receiving treatment
- O/E:
  - Vital signs normal
  - HEENT: normal
  - No peripheral synovitis, enthesitis
  - Schober's: 3.5 cm, Occiput-wall: 0 cm, Tragus-wall: 10.5 cm, Lateral spine flexion: 38 cm
  - Back pain 4/10, BASDAI 1.9
- Patient wants to restart etanercept

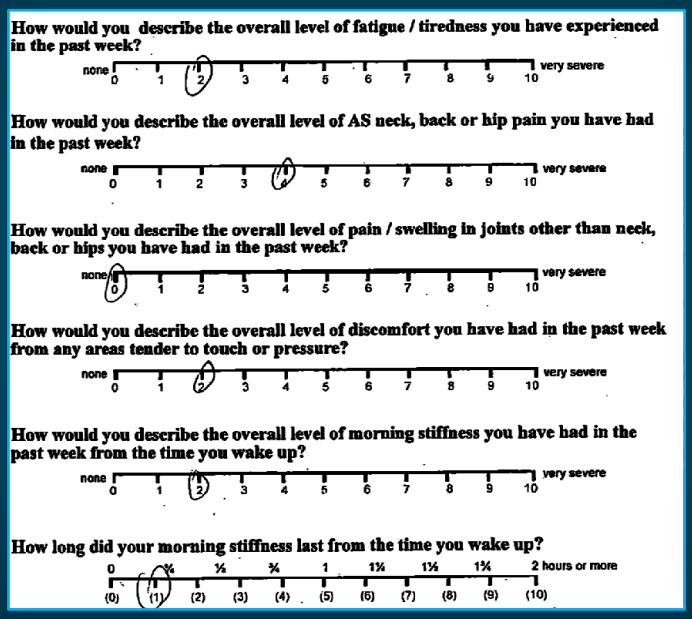
53

Imaging



54

BASDAI



How would you describe the overall level of fatigue / tiredness you have experienced in the past week?

none 0 1 2 3 4 5 6 7 8 9 10 very severe

How would you describe the overall level of AS neck, back or hip pain you have had in the past week?

none 0 1 2 3 4 5 6 7 8 9 10 very severe

How would you describe the overall level of pain / swelling in joints other than neck, back or hips you have had in the past week?

none 0 1 2 3 4 5 6 7 8 9 10 very severe

How would you describe the overall level of discomfort you have had in the past week from any areas tender to touch or pressure?

none 0 1 2 3 4 5 6 7 8 9 10 very severe

How would you describe the overall level of morning stiffness you have had in the past week from the time you wake up?

none 0 1 2 3 4 5 6 7 8 9 10 very severe

How long did your morning stiffness last from the time you wake up?

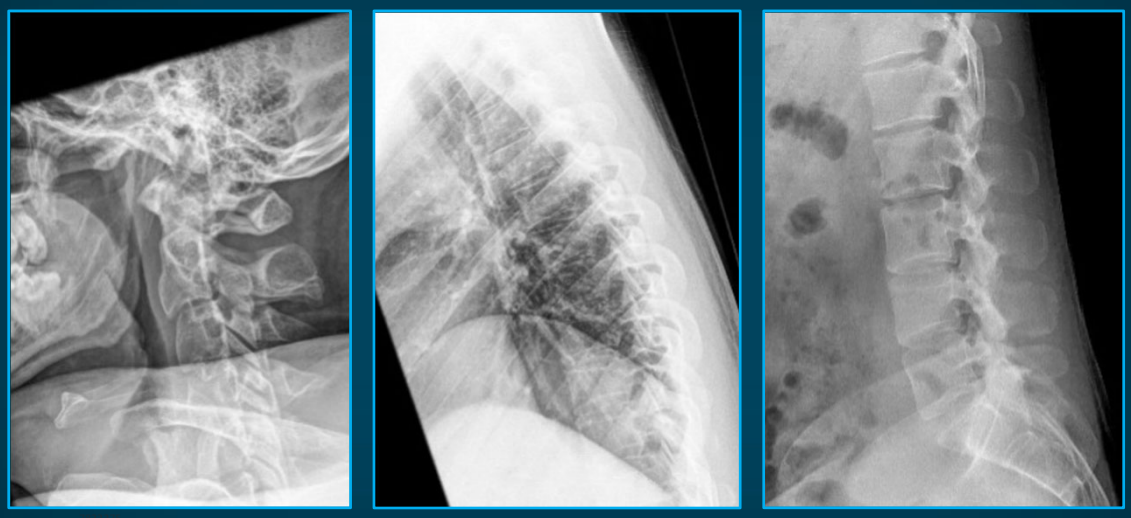
0 ¼ ½ ¾ 1 1¼ 1½ 1¾ 2 hours or more

(0) (1) (2) (3) (4) (5) (6) (7) (8) (9) (10)

BASDAI: 1.9

55

X-Rays of Cervical, Thoracic & Lumbar Spine



56

How Would You Manage This Patient?

- ***What is the next best step?***

A. Order an MRI of SI joints

B. Order ESR & CRP

C. Restart Etanercept

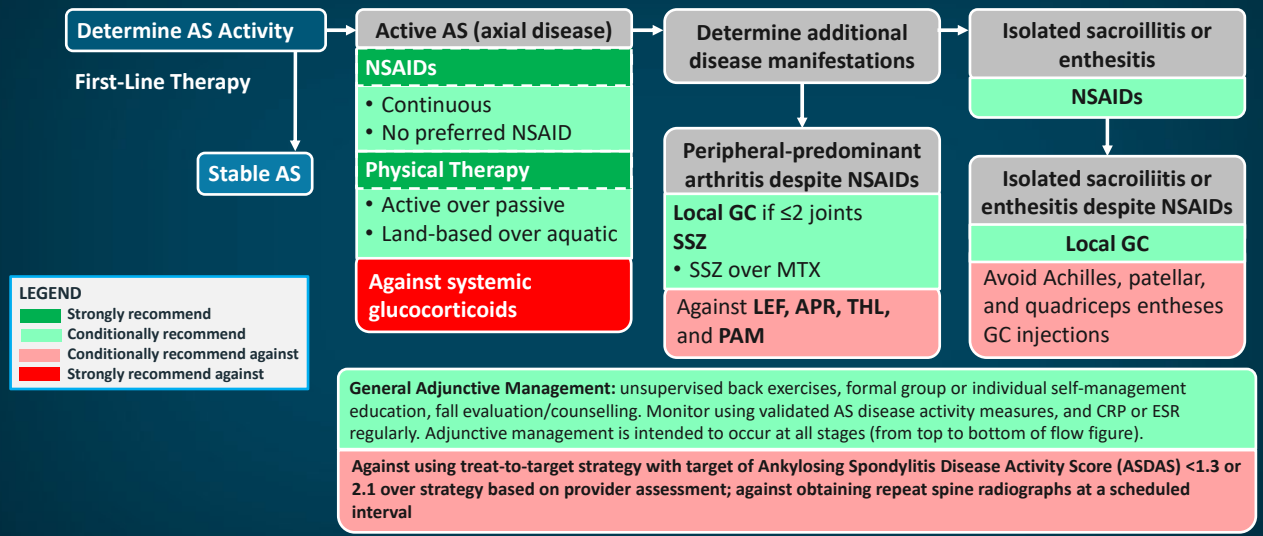
D. Start anti-TNF monoclonal antibody (he has H/O uveitis)

E. Start a NSAID on PRN basis

F. Start a full-dose NSAID

57

2019 ACR-SAA-SPARTAN Treatment Guidelines for Active AxSpA: First-Line Therapy



General Adjunctive Management: unsupervised back exercises, formal group or individual self-management education, fall evaluation/counselling. Monitor using validated AS disease activity measures, and CRP or ESR regularly. Adjunctive management is intended to occur at all stages (from top to bottom of flow figure).

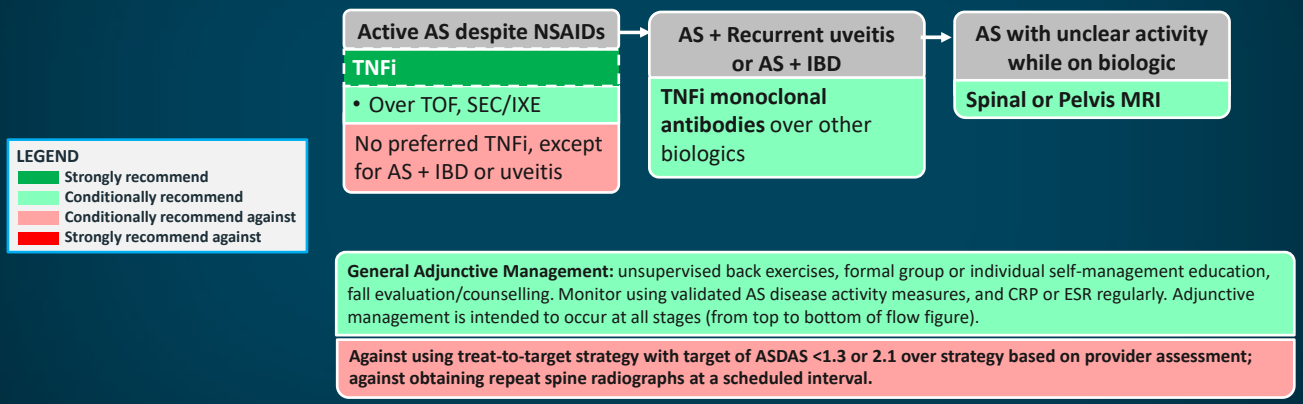
Against using treat-to-target strategy with target of Ankylosing Spondylitis Disease Activity Score (ASDAS) <1.3 or 2.1 over strategy based on provider assessment; against obtaining repeat spine radiographs at a scheduled interval

ACR = American College of Rheumatology; APR = apremilast; GC = glucocorticoid; LEF = leflunomide; MTX = methotrexate; PAM = pamidronate; PICO = population, intervention, comparison, and outcomes; SAA = Spondylitis Association of America; SPARTAN = Spondyloarthritis Research and Treatment Network; SSZ = sulfasalazine; THL = thalidomide.

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

58

2019 ACR-SAA-SPARTAN Treatment Guidelines for Active AxSpA: Second-Line Therapy



General Adjunctive Management: unsupervised back exercises, formal group or individual self-management education, fall evaluation/counselling. Monitor using validated AS disease activity measures, and CRP or ESR regularly. Adjunctive management is intended to occur at all stages (from top to bottom of flow figure).

Against using treat-to-target strategy with target of ASDAS <1.3 or 2.1 over strategy based on provider assessment; against obtaining repeat spine radiographs at a scheduled interval.

TNFi = tumor factor necrosis inhibitor; TOF = tofacitnib; SEC = secukinumab; IXE = ixekizumab.

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

59

What is the Next Best Step?

A. Order an MRI of SI joints
   Fair choice, but diagnosis is not in doubt. Would tell us about disease activity, probability of response

B. Order Sedimentation rate & CRP
   Sure, why not? But that won't satisfy him. He needs treatment for his back pain.

C. Restart Etanercept
   I wouldn't. BASDAI is low, and he hasn't had a trial of NSAIDs (either full dose or PRN) yet

D. Start anti-TNF monoclonal antibody (he has H/O uveitis)
   I wouldn't. BASDAI is low, hasn't had a trial of NSAIDs, and has no more attacks of iritis

E. Start a NSAID on PRN basis
   That's what I did – if this doesn't work, next step would be full dose NSAIDs before going to TNFi

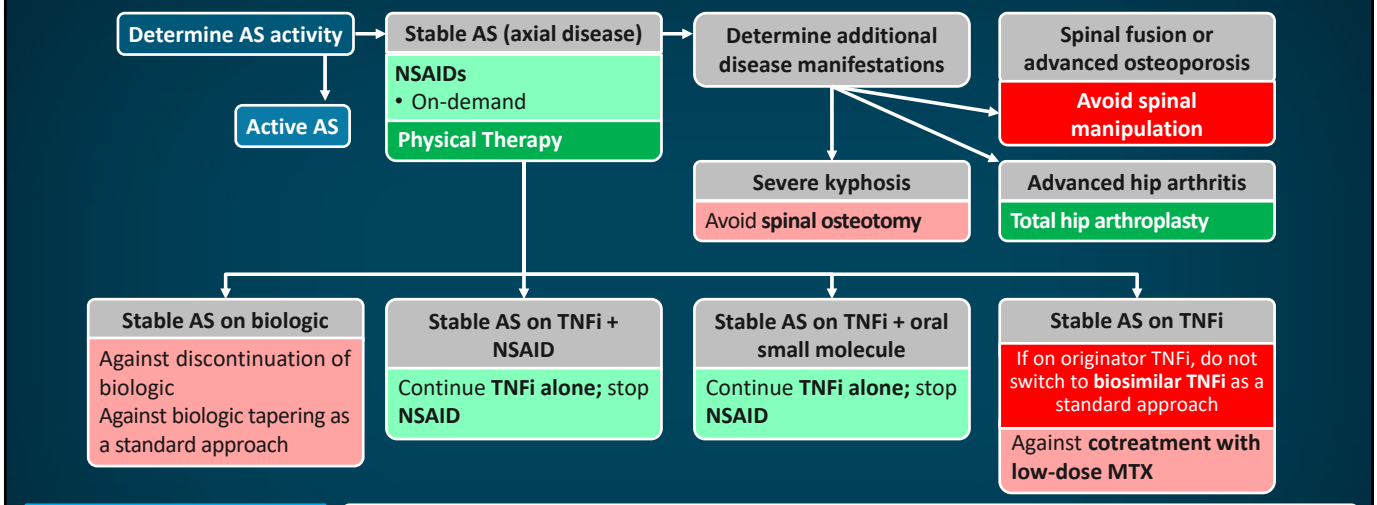
F. Start a full-dose NSAID
   Fair choice too

60

How do you approach a patient who demands a biologic when you think they can be treated with NSAIDs alone?

61

2019 ACR-SAA-SPARTAN Treatment Guidelines for Stable AxSpA



LEGEND
- Strongly recommend
- Conditionally recommend
- Conditionally recommend against
- Strongly recommend against

General Adjunctive Management: unsupervised back exercises, formal group or individual self-management education, fall evaluation/counselling. Monitor using validated AS disease activity measures, and CRP or ESR regularly.

Against obtaining spinal or pelvis MRI to confirm inactivity; Against obtaining repeat spine radiographs at a scheduled interval.

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

62

Thank you!

Q & A

63

Timely Recognition, Management, and Referral of Axial Spondyloarthritis

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