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Precision Medicine in Ankylosing Spondylitis:

Fine-tuning Diagnosis and Treatment

APRIL 20, 2018

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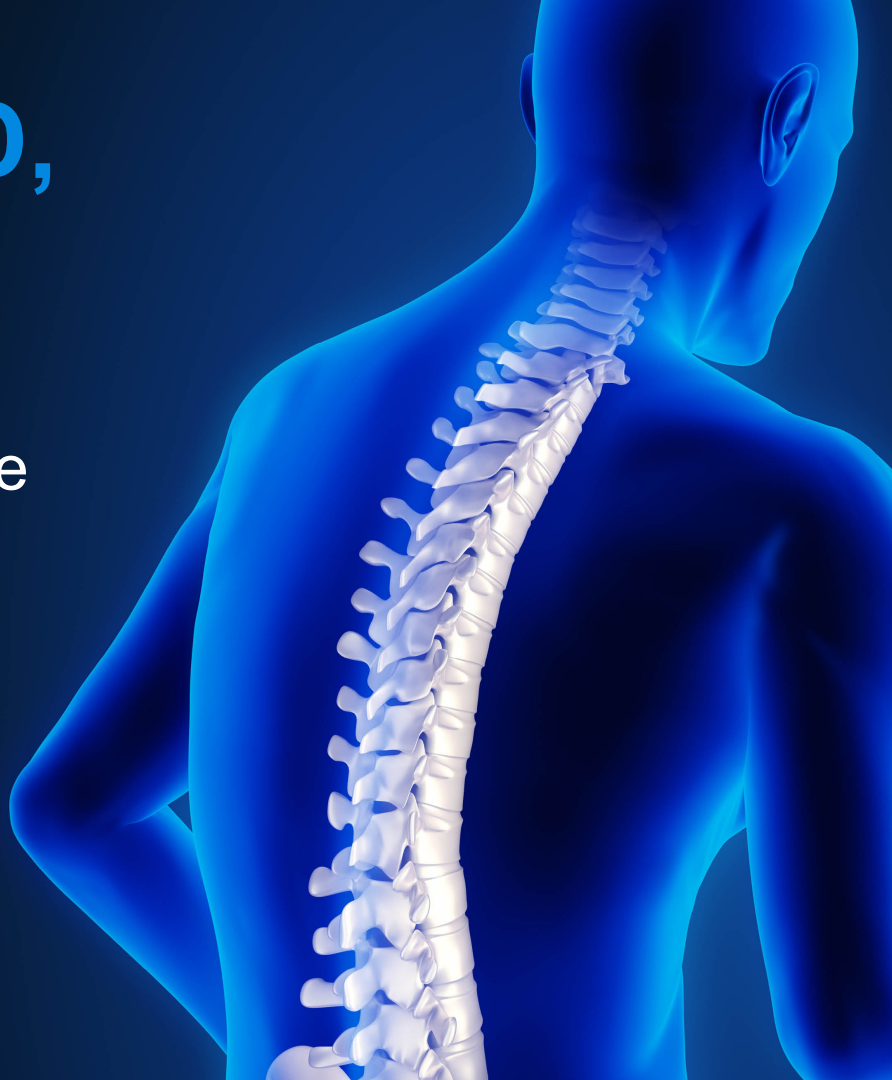

Joerg Ermann, MD

Instructor in Medicine
Brigham and Women's Hospital
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Boston, MA

Learning Objective 1

Recognize key clinical features of ankylosing spondylitis (AS) to aid in timely diagnosis.

Learning Objective 2

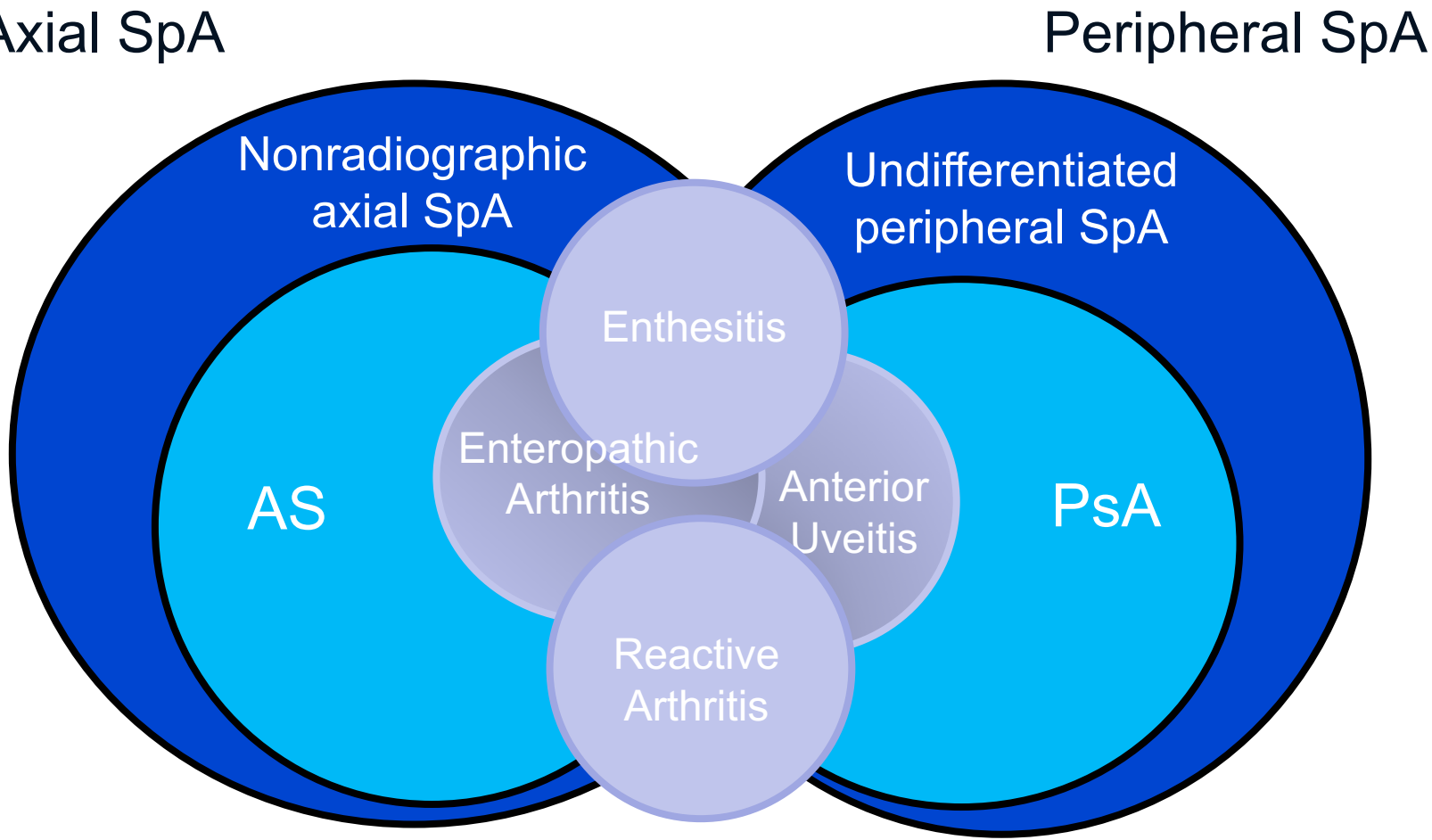
Incorporate classification criteria and diagnostic tests into clinical practice to support early detection of AS.

Learning Objective 3

Implement biologic treatments for AS into clinical practice when appropriate.

Learning Objective 1

Recognize key clinical features of ankylosing spondylitis (AS) to aid in timely diagnosis.



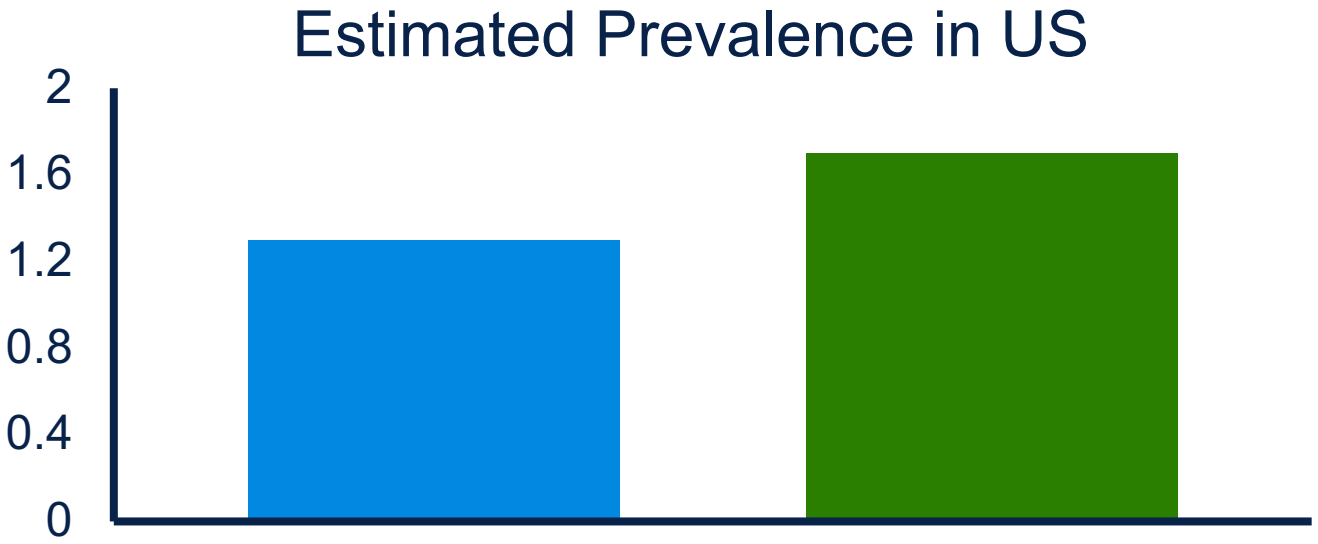
Courtesy Muhammad Asim Khan, MD

Ozgocem S, et al. *Curr Rheumatol Rep.* 2012;14(5):409-414.; van Turbergen A, et al. *Nat Rev Rheumatol.* 2012;8(5):253-261.

Ankylosing Spondylitis (AS)

- An inflammatory arthritis within a family of related spondylarthritides (SpA) which includes psoriatic arthritis (PsA) and others
- Prevalence in United States is 0.1-1.4%
- Patients may often have other extra-articular manifestations (EAMs) that are linked to increased disability and healthcare expenditures
  - Uveitis, IBD, psoriasis

More People Are Afflicted with SpA Diseases than with Rheumatoid Arthritis (RA)

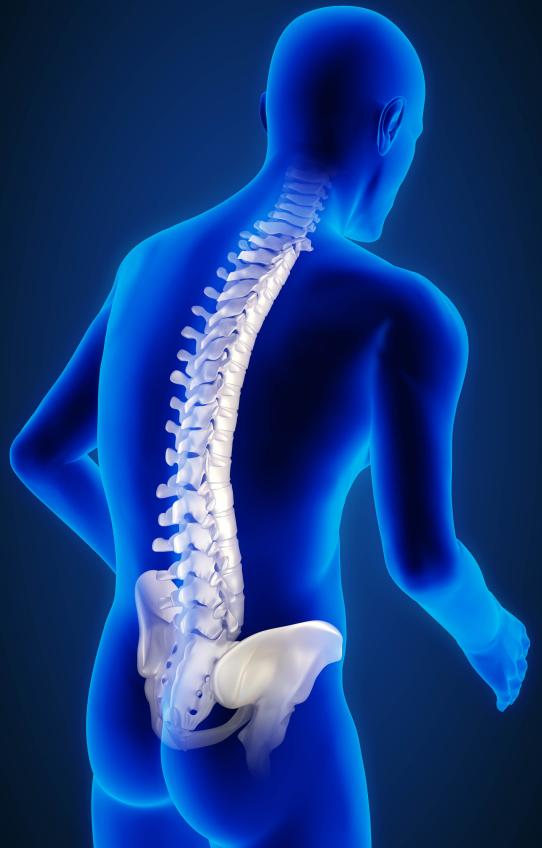


Helmick CG, et al. *Arthritis Rheum.* 2008;58(1):15-25.; Reveille JD, et al. *Arhritis Care Res.*. 2012;64(6):905-910.

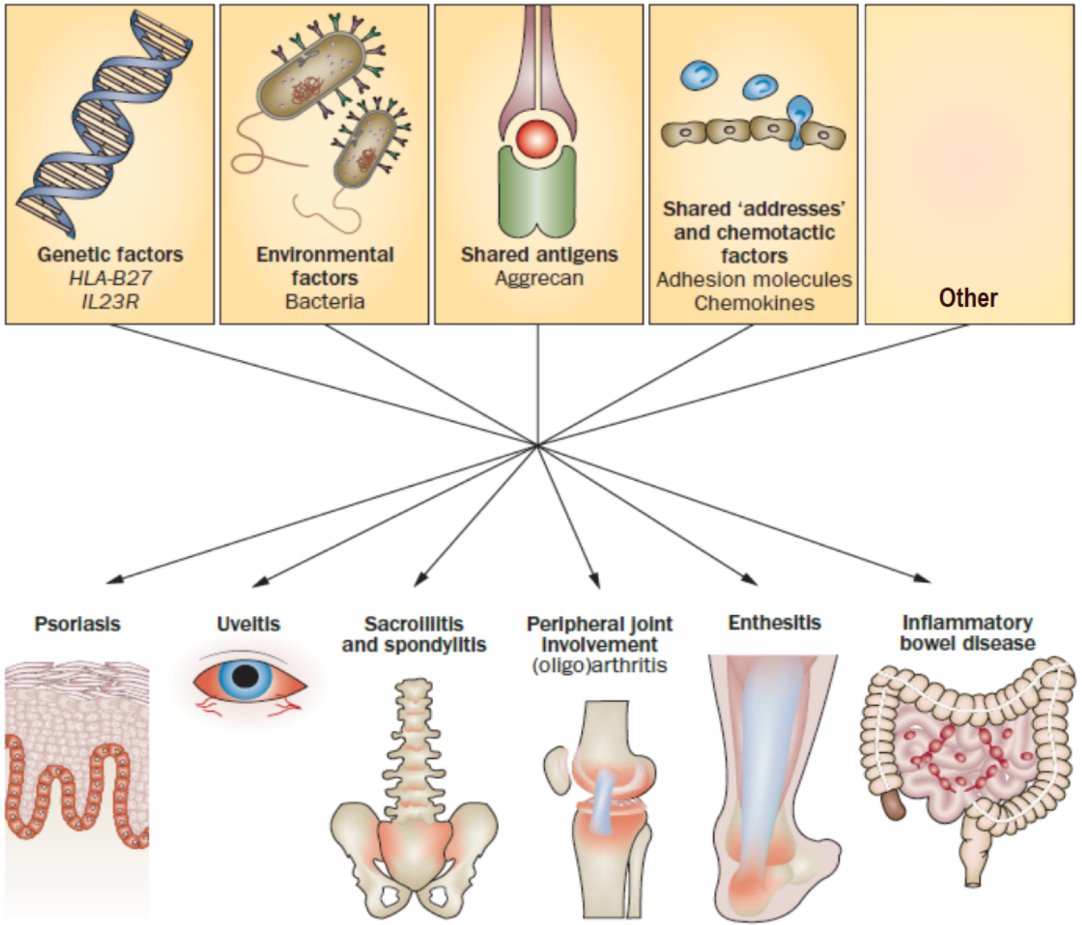
Audience Response

Which of these is a possible clinical manifestation seen in AS?

A. Glomerular nephritis
B. Uveitis
C. Migraine headache
D. Oral ulcers
E. I’m not sure



Factors Linked to Spondyloarthritis (SpA)



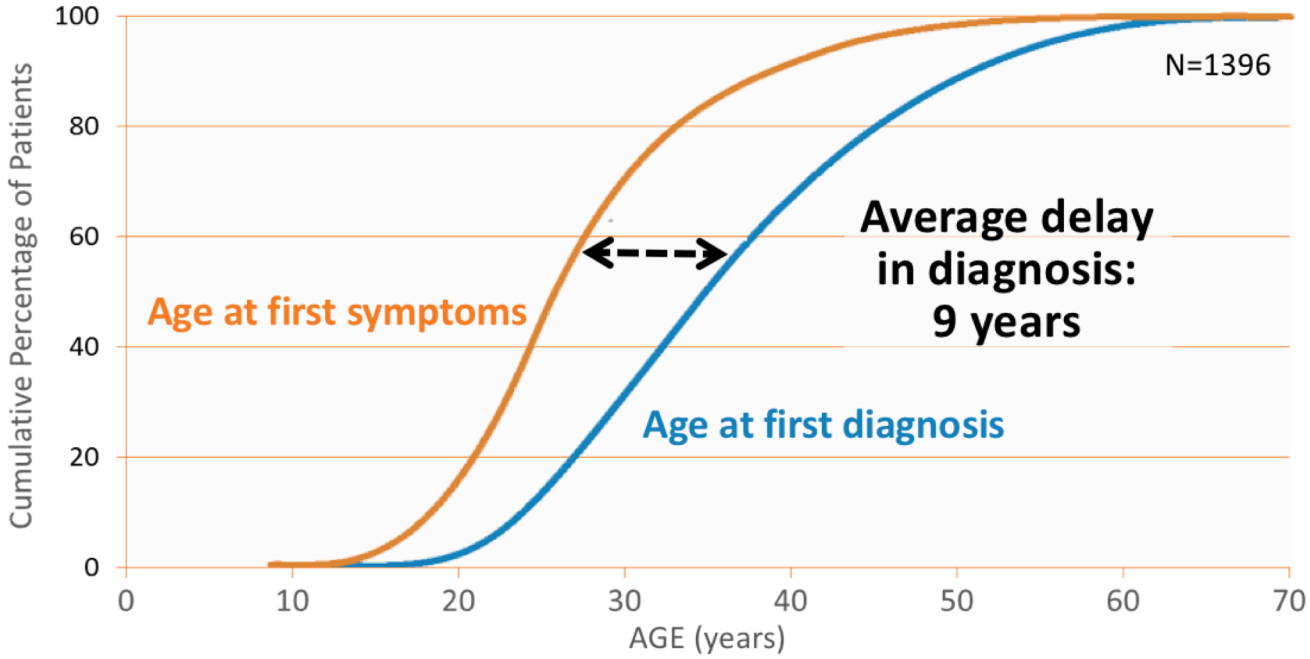
Rosenbaum JT, et al. *Nat Rev Rheumatol* . 2012;8(5):249-250.

HLA-B27

- Allele of the HLA-B locus
  - Association with AS described in 1973 (~90%)
- Also associated with other types of SpA
  - PsA: 40-50%
  - Reactive arthritis: 30-70%
- 6.1% of US population are HLA-B27+
  - 7.5% non-Hispanic White
  - 4.6% Mexican American
  - 1.1% non-Hispanic Black

Khan MA. *Curr Rheumatol Rev.* 2010;12:337-341.
Reveille JD, et al. Arthritis Rheum 2011,64;(5):1407-1411.

Age at First Symptoms and Diagnosis in Patients with AS



Significantly longer delay in diagnosis in women vs. men 9.8 vs. 8.4 yrs ($p < 0.01$)

Feldtkeller E, et al. *Curr Opin Rheumatol.* 2000.12(4):239-247

Speaking as a patient or on behalf of your AS patient community, how many MDs did you have to visit, and how long did it take on average, to receive an accurate diagnosis of AS?

"I saw 7 MDs in my search to discover that I had AS. It took 7 physicians and 6 years."

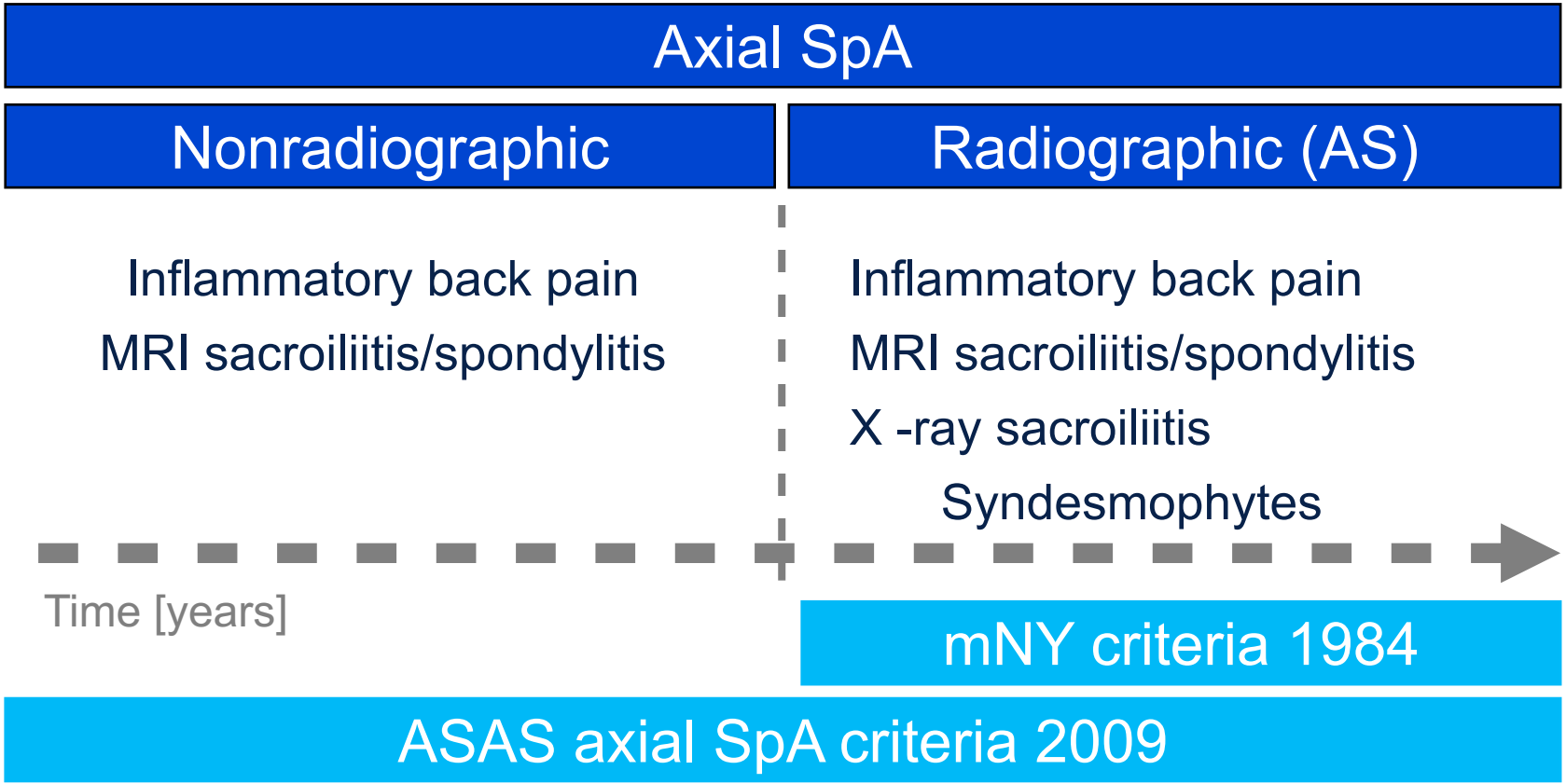
"I saw at minimum 15-20 doctors in the various parts of the country that I lived in over about a 13 year span."

"Approximately 4 physicians and 20 years."

"6 doctors, I went to 2 primary care physicians, 2 rheumatologists, I went to an emergency room MD, and I finally went to an ophthalmologist. So I guess 7."

Inflammatory Back Pain

Feature	Mechanical	Inflammatory
Age of onset	> 40 years	< 45 years
Onset	Acute	Insidious
Worst time of day	End of the day	Morning
Morning stiffness	None or < 30 minutes	> 30 minutes
Nocturnal back pain	When going to bed	2nd part of night
Exercise / activity	Usually worse	Makes pain better
NSAIDs improve pain	15%	80%
Associated with sciatica	Can be	Not usually



van der Linden S, et al. *Arthritis Rheum* 1984;27(4):361-368.; Rudwaleit M. *Ann Rheum Dis* 2009;68:777-783.

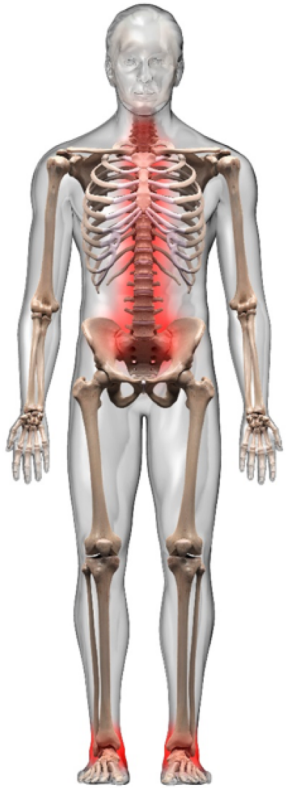
AS in Clinical Practice

Clinical signs and symptoms of systemic inflammation	Objective measures of systemic inflammation	Other factors
• Inflammatory back pain • Arthritis • Enthesitis • Inflammatory bowel disease • Psoriasis • Dactylitis • Uveitis	• Radiographic evidence of join damage • Acute phase reactants such as ESR or CRP	• Family history of SpA disease • HLA-B27

Assess the full range of symptoms to determine a timely diagnosis and appropriate management plan

Amor B, et al. *J Rheumatol.* 1995;21(10):1883-1887.; van Tubergen A, et al. *Nat Rev Rheumatol.* 2012;8(5):253-261.

Closely Evaluate Key Features of AS



Apparent Signs of Inflammation	Hidden Signs of Inflammation
Skin	
• 11% of AS patients have psoriatic involvement	• Patients initially may not notice signs of skin involvement, which can often occur behind the ear, on the back, scalp or in the gluteal fold
Gut	
• ~1% - 6% of AS patients have UC/CD	• 26%-69% of AS patients have subclinical gut inflammation, not related to GI complaints
Joints	
• Inflammation can affect multiple joins simultaneously or randomly	• 25% of AS patients have peripheral involvement • Early changes on conventional radiographs include squaring of vertebral bodies & formation of syndesmorphytes

Baeten D, et al. *Best Pract Res Clin Rheumatol.* 2002;16(4):53—549; Edmunds L, et al. *J Rheumatol*. 1991;18(5):696-698.; Elyan M, et al. *J Rheumatol*. 2006; 3(suppl 78):12-24.; Gladman DD, et al. *Ann Rheum Dis*. 2005;64(suppl 11):ii14-ii17.; Khan MA. *Atlas of Rheumatology 4th Ed.* 2005;151-181.; Smale S, et al. *Arthritis Rheum.* 2001;44(12):2728-2736.; Vander Cruyssen B, et al. *Ann Rheum Dis.* 2007;66:1072-1077.

Learning Objective 2

Incorporate classification criteria and diagnostic tests into clinical practice to support early detection of AS.

Distinctions Between Classification Criteria and Diagnostic Criteria

Classification criteria	Diagnostic criteria
• Intended to create well-defined, homogeneous cohorts of patients for clinical research • Favor specificity over sensitivity	• Guide the care of individual patients • Include patients with unusual presentations • Performance depends on context

Aggarwal R, et al. *Arthritis Care Res* 2015;67:891-897.

Classification Criteria for AS: 1984 Modified New York Criteria

- Clinical criteria:
  - Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest.
  - Limitation of motion of the lumbar spine in the sagittal and frontal planes.
  - Limitation of chest expansion relative to normal values correlated for age and sex.
- Radiological criterion:
  - Sacroliitis grade ≥ 2 bilaterally or grade 3-4 unilaterally
- Definite AS if the radiological criterion is associated with at least one clinical criterion

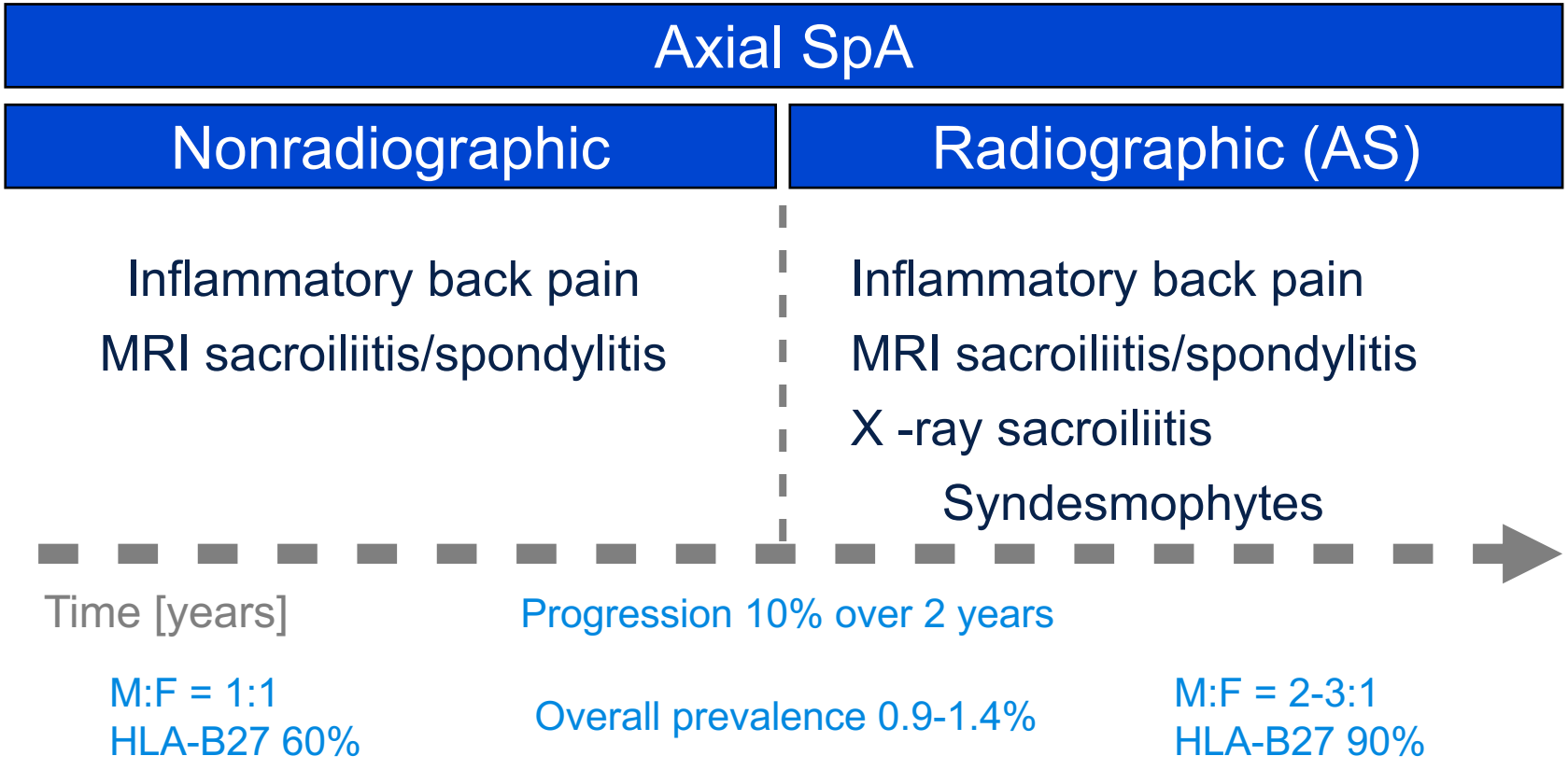
van der Linden S, et al. *Arthritis Rheum.* 1984;27(4):361-368

ASAS Classification Criteria for axial SpA

In patients with ≥ 3 months back pain and age of onset < 45 years

Sacroiliitis on Imaging plus ≥ 1 SpA Feature	OR	HLA-B27 plus ≥ 2 Other SpA Feaures
SpA features • 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		Sacroiliitis on imaging • Active (acute) inflammation on MRI highly suggestive of sacroiliitis associates with SpA • Definite radiographic sacroiliitis according to modified NY criteria* *Radiographic sacroiliitis confirms diagnosis of AS

N = 649 patients with back pain.
Sensivtivity: 82.9%, Specificity: 84.4%.; Imaging alone: Sensitivity: 66.2%, Specificity: 97.3%
Elevated CRP is considered a SpA feature in the context of chronic back pain.
Rudwaleit M, et al *Ann Rheum Dis* 2009;66:777-783.



Risk factors for progression: male, high inflammatory activity, HLA-B27, smoking

van der Linden S, et al. *Arthritis Rheum.* 1984;27(4):361-368.; Rudwaleit M. *Ann Rheum Dis.* 2009;68:777-783.

Diagnosing Axial SpA/AS

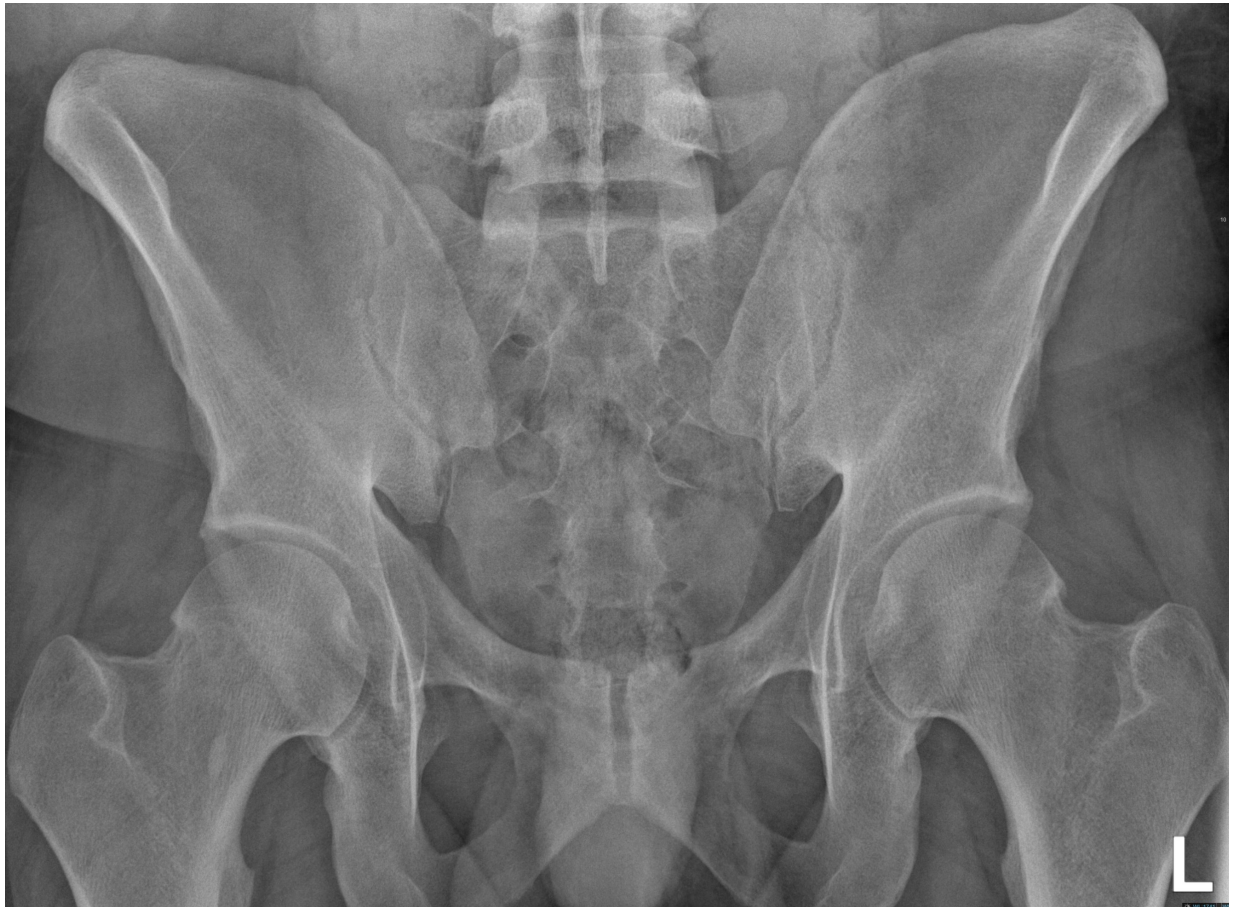
1. A thorough history is critical
2. Diagnostic testing: CRP, HLA-B27, pelvic radiograph (single view) followed by MRI of SI joints (STIR) if negative
3. A positive HLA-B27 test never makes a diagnosis
4. A negative HLA-B27 test or negative MRI of the SI joints do not rule out a diagnosis
5. The more SpA features are present, the higher the likelihood of axial SpA

When to Refer?

Patients with chronic back pain (duration ≥3mos) with back pain onset before age of 45 should be referred to rheumatologist if at least one of the following parameters is present:

- Inflammatory back pain
- HLA-B27 positive
- Sacrolitis on imaging
  - Xrays or MRI
- Peripheral mainfestations
  - Arthritis, ethesitis, and/or dacytilitis
- Extra-articular manifestations
  - Psoriasis, IBD, and/or uveitis
- Positive family history of ankylosing spondylitis
- Good response to NSAIDs
- Elevated acute phase reactants

Poddubnyy D, et al. *Ann Rheum Dis.* 2015;74(8):1483-1487.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Speaking as a patient or on behalf of your AS patient community, did you feel like your PCP adequately communicated to you the tests they wanted to do; and if you were referred to a specialist, did you feel multiple tests were being duplicated or that incorrect tests were being done?

"No, I did not feel like I had a good understanding of the testing that was done and I get the same feeling from my community. Some doctors, whether they are PCPs or rheumatologists, kind of throw out tests just to see what sticks."

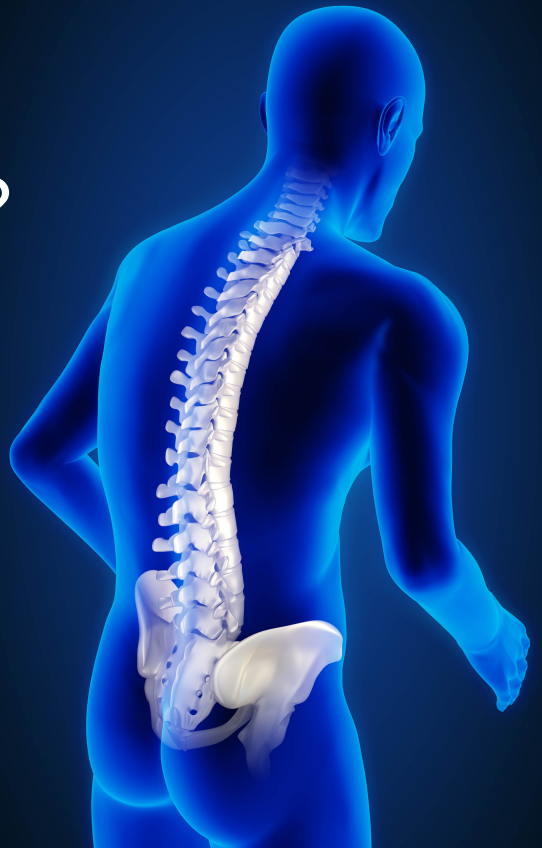
"My PCP did not do any tests. I was referred to an ophthalmologist because of my eye pain. The eye pain was triggering the doctor to look at the blood test HLA-B27 which diagnosed that I had AS."

"No, the possibility of me having arthritis or inflammatory arthritis was never addressed by my PCP. I had asked for several tests just trying to get an understanding of what was going on, if it was lupus or some other form of inflammatory arthritis, but I wasn't able to receive those test, I was never referred to a rheumatologist…."

Audience Response

Which of the following should be considered first line therapy for AS?

A. Indomethacin
B. Methotrexate
C. Etanercept
D. Secukinumab
E. I’m not sure



Learning Objective 3

Implement biologic treatments for AS into clinical practice when appropriate

ASAS/EULAR Recommendations for Management of AS

- Patient education
- Exercise
- Physical therapy
- Rehabilitation
- Patient associations and self-help groups

NSAIDs

Axial involvement

Peripheral joint involvement

Sulfasalazine

Local corticosteroids

TNF antagonists

Analgesics

Surgery

Zochling I, et al. *Ann Rheum Dis.* 2006;65(4):442-452.

Management of Active Axial SpA/AS

- NSAIDs + PT are first-line therapy
- start TNFi if disease remains active on NSAIDs
  no preference for specific NSAIDs or TNFi
  (except uveitis, IBD)
- TNFi failure
  - switch to alternative TNFi OR
  - switch to IL-17A inhibitor

Ward MM, et al *Arthritis Rheumatol* 2016;68:282-298.; van der Heijde D, et al. *Ann Rheum Dis* 2017;76:978-991.

Exercise and Physical Therapy in Axial SpA/AS

- Cochrane review 2008:
  - Inpatient spa-exercise therapy followed by group PT > group PT > individual home-based exercises > no intervention
- Practical recommendations:
  - Spinal extension + deep breathing exercises twice daily
  - Maintain proper posture
  - Sleep on firm mattress without pillow
- Consider degree of spinal involvement:
  - Avoid contact and other risk sports in patients with ankylosis - no restrictions in non-radiographic axial SpA

Dagfinrud H, et al. *Cochrane Database Syst Rev* 2008;(1):CD002822.; Elyan M, et al. *Curr Rheumatol Rep.* 2006;8;(4): 255-259.

Speaking as a patient or on behalf of your AS patient community, did your clinician explain to you the need to slow radiographic progression of your disease and how that drives your treatment?

"Neither of them explained the process to me, the prognosis of the disease or how it affects people on or off medicine, or things I can do on my own to slow the progression without medicine. I felt very much alone and I think a lot of the people in my community online or Facebook groups of 20,000 members feel the same."

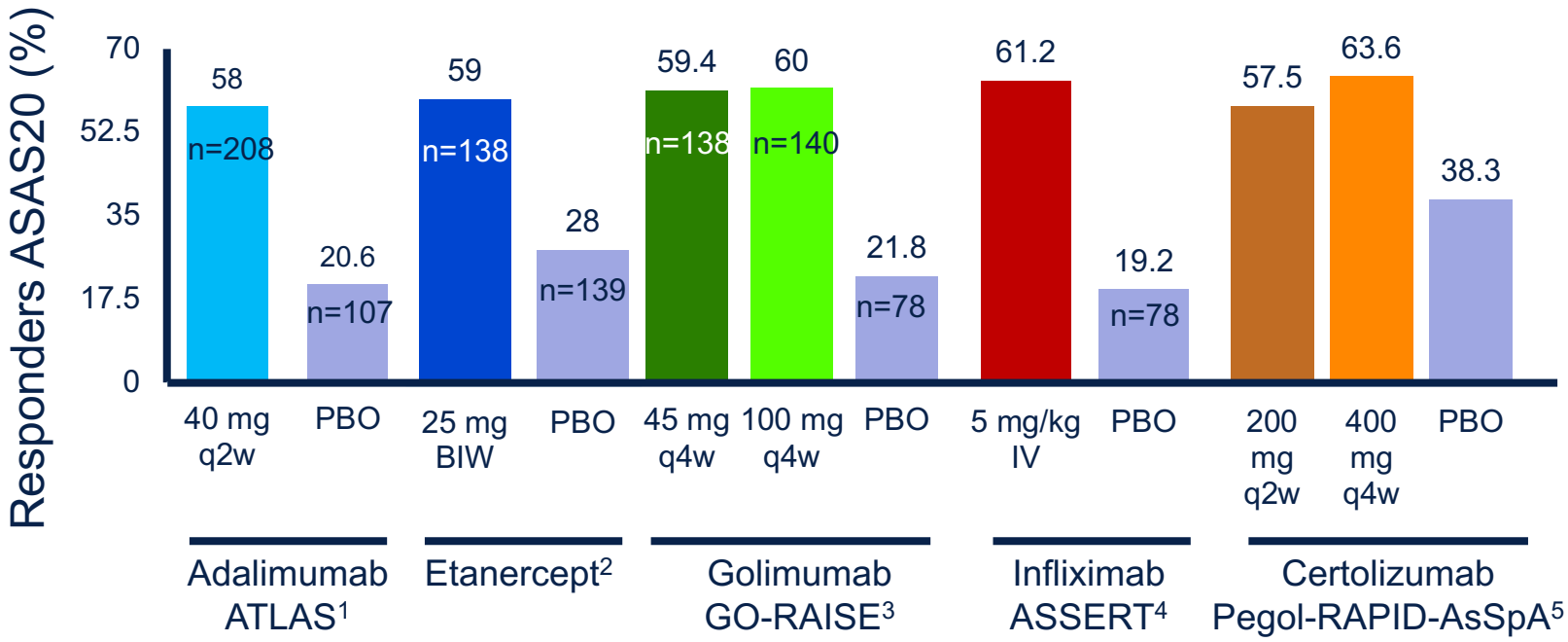
"No it was not explained to me. However, I've done a fair amount of research on my own talking to other healthcare professionals. I'm aware of what drives my treatment but it wasn't clearly explained."

"I was not necessarily told about stopping radiographic progression, only that I needed to start on the oldest and cheapest form of treatment until we found one that had success. That did cause a year of medications that did not work or that I had severe reactions too…

Ankylosing Spondylitis: When NSAIDs Aren't Enough

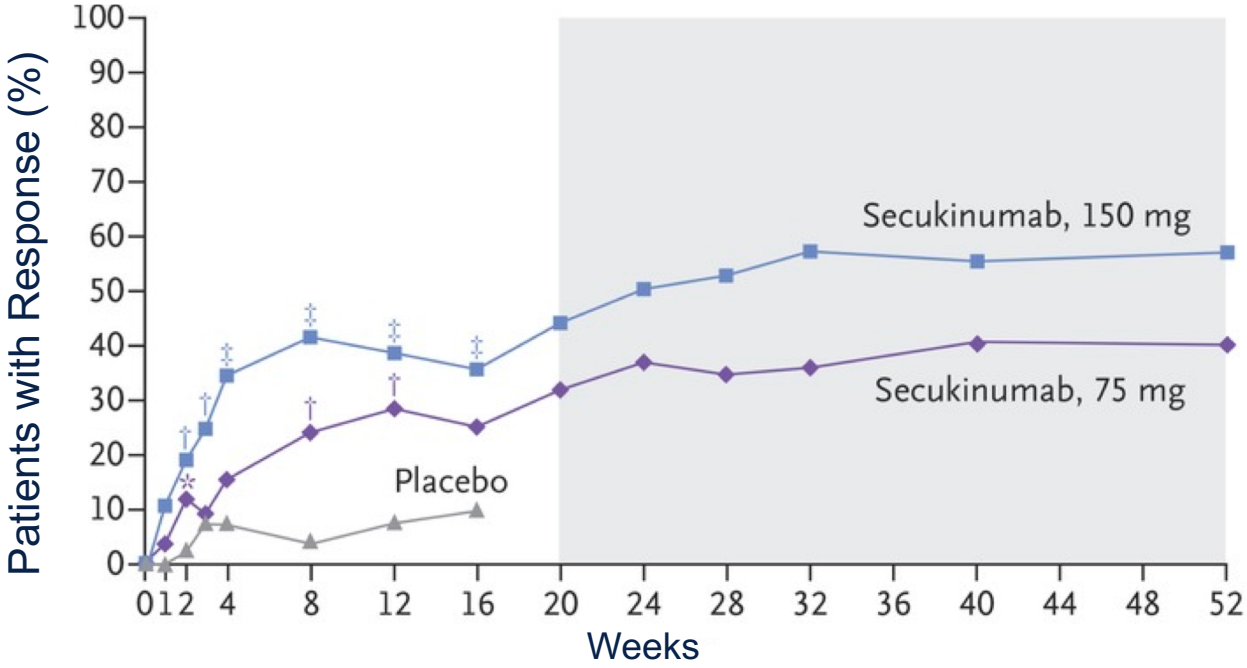
Agent	Target
Adalimumab	TNF Inhibitor
Certolizumab	TNF Inhibitor
Etanercept	TNF Inhibitor
Golimumab	TNF Inhibitor
Infliximab	TNF Inhibitor
Secukimumab	IL-17A inhibitor

TNF inhibitors in Ankylosing Spondylitis



1. van der Heijde *Arthritis Rheum* 2006;54:2136-46, 2. Davis *Arthritis Rheum* 2003;48:3230-6, 3. Inman *Arthritis Rheum* 2008;58:3402-3412, 4. van der Heijde *Arthritis Rheum* 2005;52:582–591.; 5.Landewé *Ann Rheum Dis* 2014;573:39–47.

Secukimumab: Efficacy at 52 Weeks



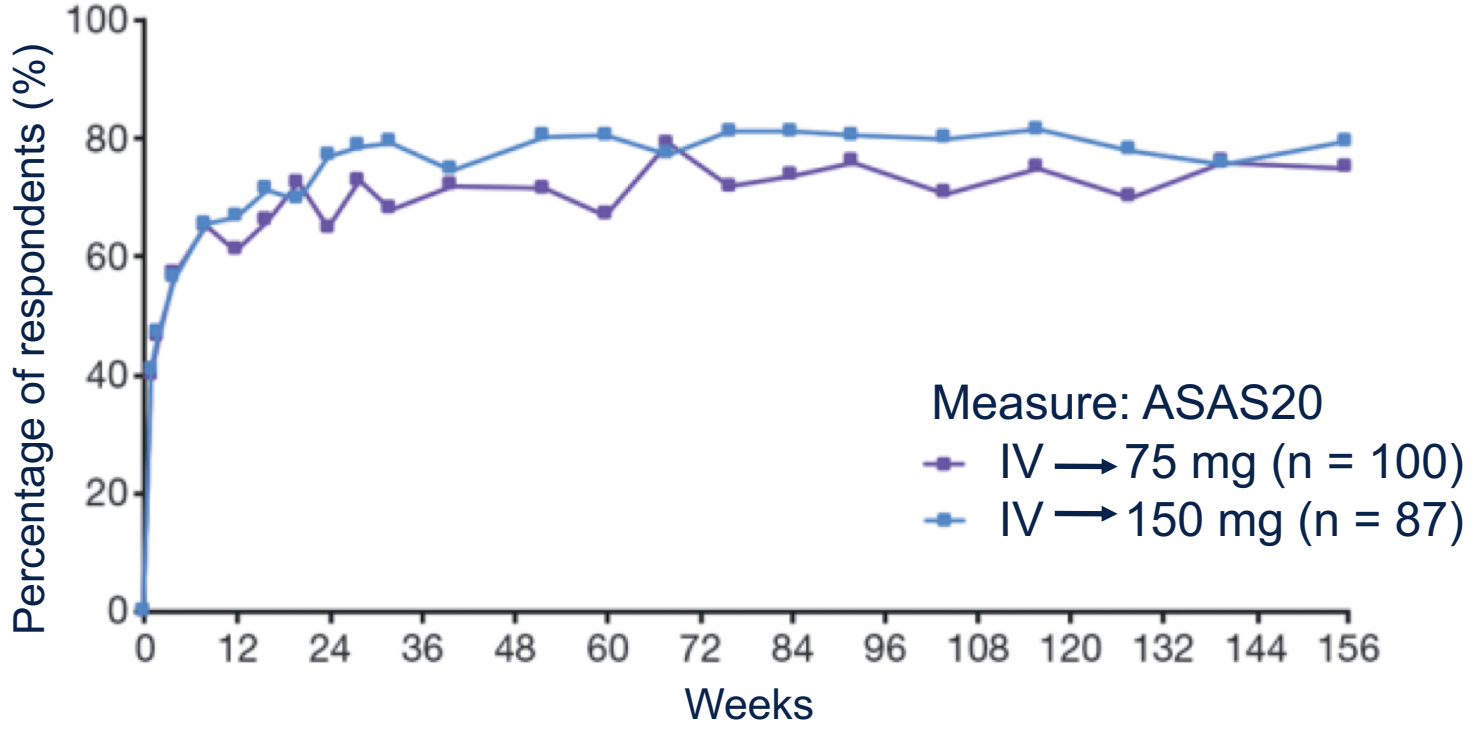
Measure: ASAS40

No. of Patients

	Wk 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 40	Wk 52
Secukinumab 150 mg	72	72	72	72	72	65	65	62	63	63	61
Secukinumab 75 mg	73	73	73	73	73	68	87	68	66	64	61
Placebo	74	74	74	74	74						

Baeten D, et al. *N Engl J Med.* 2015; 373:2534-2548.

Secukimumab: 3 Year Efficacy

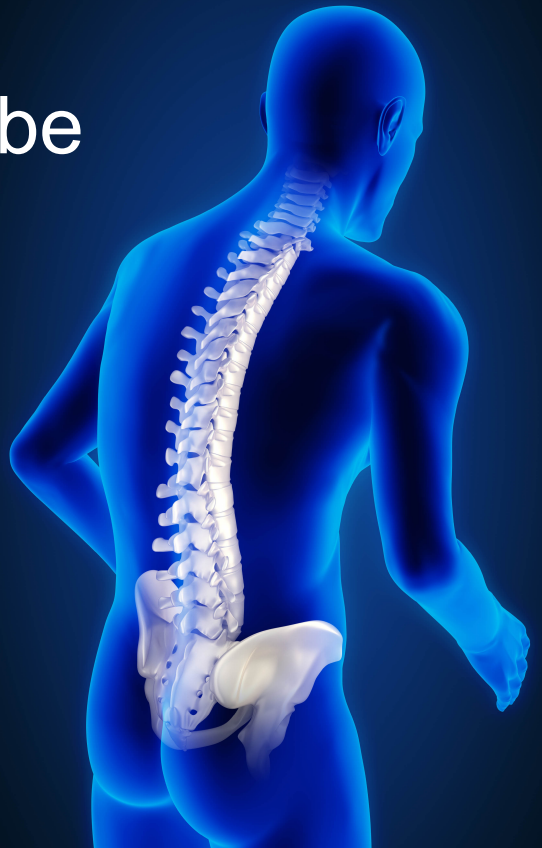


Baraliakos X, et al. *Clin Exp Rheumatol*. 2018;36(1):50-55.

Audience Response

How often should HLA-B27 testing be done?

A. Monthly
B. Whenever therapy is changed
C. Annually
D. Never
E. I’m not sure



What to Look For

- Infections
  - Especially opportunistic (e.g. mucocutaneous candidiasis, TB)
- Malignancy
- Fracture

Infection Prevention

- No live vaccines on biologics
- Annual inactivated influenza vaccination
- 2017 Advisory Committee on Immunization Practices (CDC) recommendations: both pneumococcal 13-valent conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23) plus booster are recommended

13-valent pneumococcal conjugate vaccine (PCV13 [Prevnar 13].; 23-valent pneumococcal polysaccharide vaccine (PPSV23 [Pneumovax 23].; Pneumococcal 13-valent conjugate vaccine. Product information. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM201669.pdf. Accessed April 18, 2018; Pneumococcal vaccine polyvalent. Product information. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM257088.pdf. Accessed April 18, 2018. Centers for Disease Control and Prevention. Adult Immunization Schedule. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html. Accessed April 18, 2018. Centers for Disease Control and Prevention. Adult Immunization Schedule. https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html. Accessed April 18, 2018

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Recognize key clinical features of ankylosing spondylitis (AS) to aid in timely diagnosis.
- Incorporate classification criteria and diagnostic tests into clinical practice to support early detection of AS.
- Implement timely referral for rheumatology evaluation if any suspicion for axial SpA/AS.
- Together with the rheumatologist, co-manage the patient with AS to reinforce goals of treatment and monitor for adverse events

Questions & Answers

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