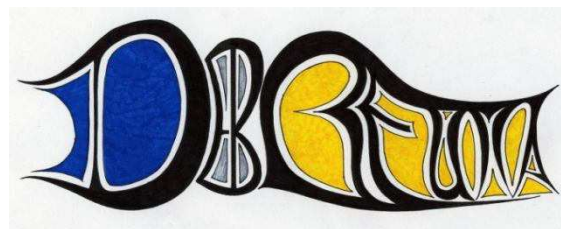


Inflammation and new bone formation in ankylosing spondylitis

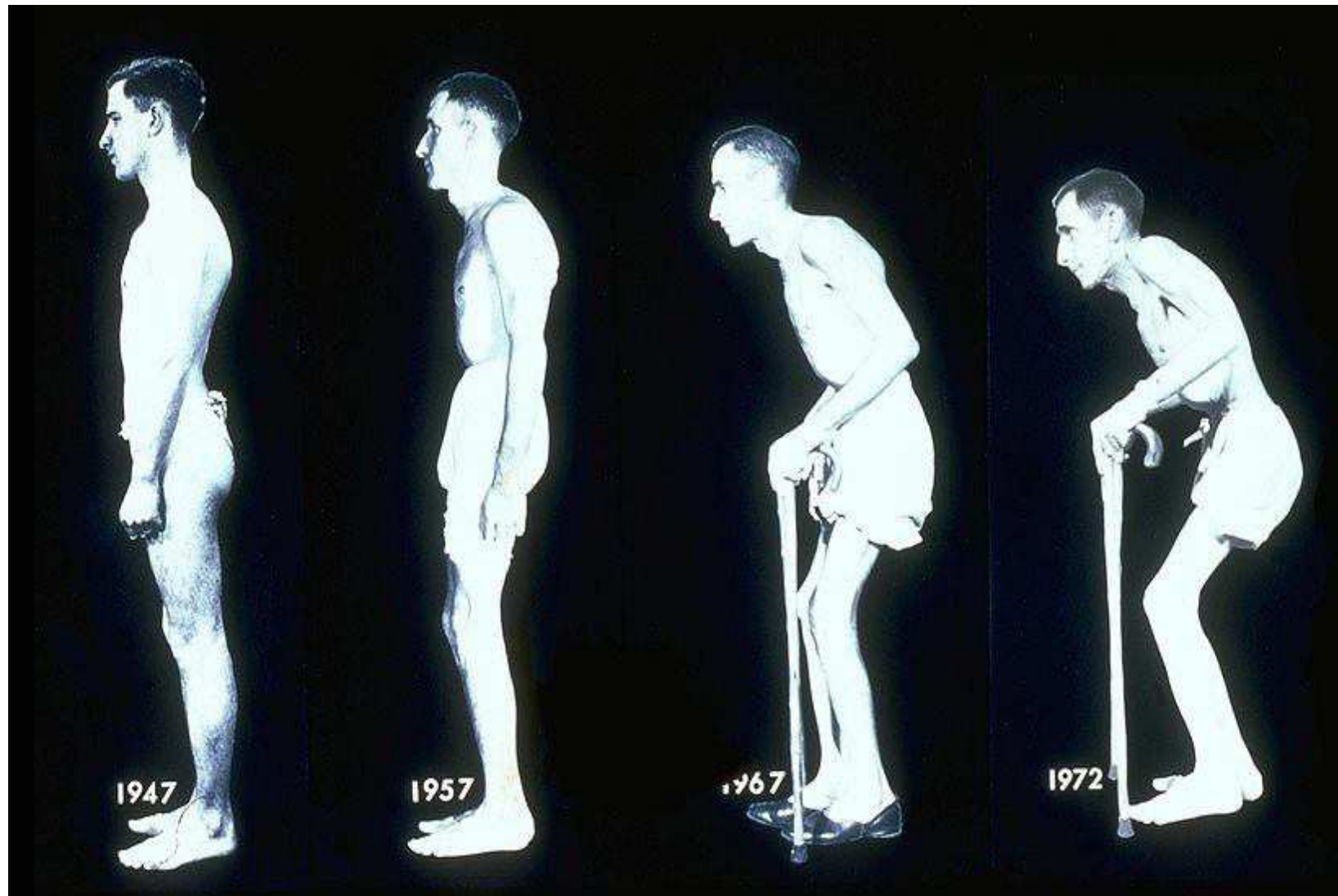
Sandor Szanto

University of Debrecen, Clinical Center, Department of Rheumatology

3rd Kosice-Debrecen Rheumatology Meeting, 2014
16-17th May 2014



Ankylosing spondylitis (AS)



Little H et al. Am Med J. 1976;60:279-85.

Modified New York Criteria for Ankylosing Spondylitis (1984)

1. Clinical criteria:

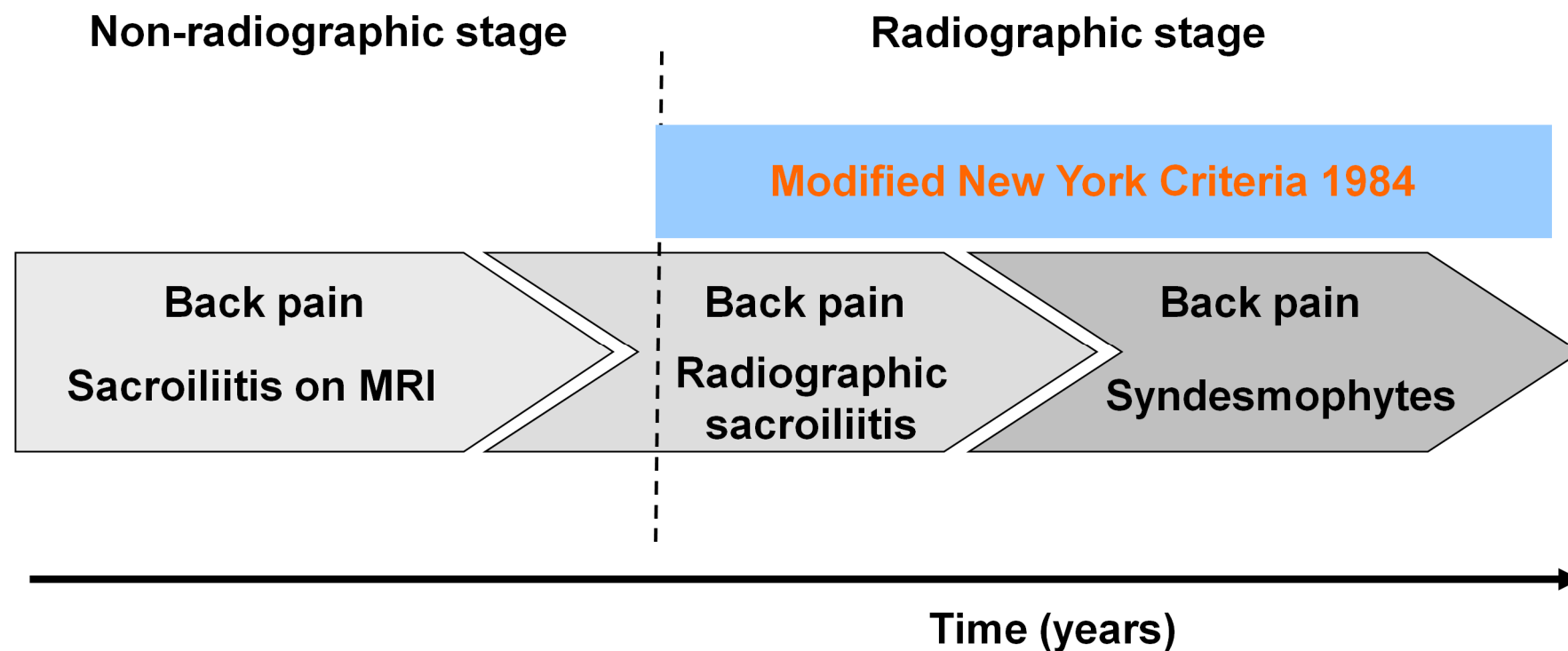
- a. Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest.
- b. Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
- c. Limitation of chest expansion relative to normal values correlated for age and sex.

2. Radiological criterion:

Sacroiliitis grade ≥ 2 bilaterally or grade 3-4 unilaterally

Definite ankylosing spondylitis if the radiological criterion is associated with at least 1 clinical criterion.

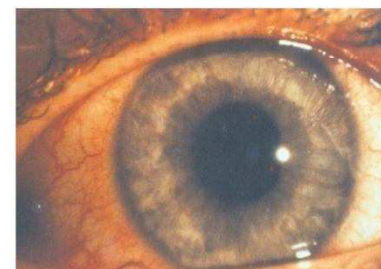
Axial Spondyloarthritis



Spondyloarthritis: Characteristic Parameters Used for Diagnosis I

Symptoms

Inflammatory
back pain



Imaging



Lab

ESR/CRP

Patient's history

Good response to NSAIDs

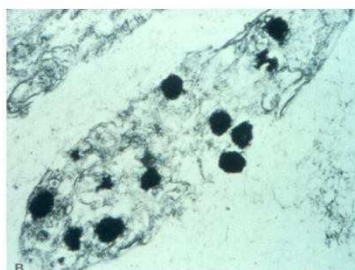
Spondyloarthritis: Characteristic Parameters Used for Diagnosis II

Genetics

HLA-B27
positive

family
history

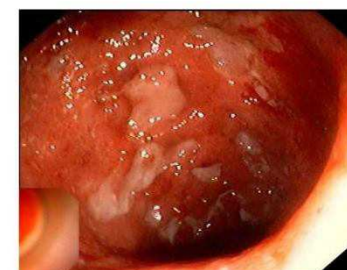
Predisposing/
concomitant
diseases



Infection*



psoriasis



Crohn's

*positive staining for Chlamydia in synovial membrane¹

1. Schumacher HR et al. Arthritis Rheum 1988;31:937-946

Ankylosing Spondylitis / Axial Spondyloarthritis

Typical Manifestations

	Sensitivity	Specificity	LR+	LR-
• inflammatory back pain	71-75 %	75-80 %	3.1	0.33
• enthesitis (heel pain)	16-37 %	89-94 %	3.4	0.71 [†]
• peripheral arthritis	40-62 %	90-98 %	4.0	0.67 [†]
• dactylitis	12-24 %	96-98 %	4.5	0.85 [†]
• anterior uveitis	10-22 %	97-99 %	7.3	0.80 [†]
• psoriasis	10-20 %	95-97 %	2.5	0.94 [†]
• inflammatory bowel disease	5-8 %	97-99 %	4.0	0.97 [†]
• positive family history for SpA	7-36 %	93-99 %	6.4	0.72
• good response to NSAIDs	61-77 %	80-85 %	5.1	0.27
• elevated acute phase reactants	38-69 %	67-80 %	2.5	0.63
• HLA-B27 (axial involvement)	83-96 %	90-96 %	9.0	0.11
• Sacroiliitis on MRI	60-85 %	90-97 %	20.0*	0.41
• Sacroiliitis (≥ grade 3) on x-rays	40%	98 %	20.0*	0.61

* best estimate

Positive likelihood ratio (LR+) = sensitivity / (100 – specificity)

Negative likelihood ratio (LR-) = (100 – sensitivity) / specificity

† It is recommended to ignore a negative test result of these tests in an early state of possible axial SpA

Modified from: Rudwaleit M et al. Ann Rheum Dis 2006;65:1251-2



ASAS Classification Criteria for Axial Spondyloarthritis (SpA)

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

Sacroiliitis on imaging*
plus
 ≥ 1 SpA feature

OR

HLA-B27
plus
 ≥ 2 other SpA features

*Sacroiliitis on imaging

- active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- definite radiographic sacroiliitis according to the modified New York criteria

SpA features:

- inflammatory back pain
- arthritis
- enthesitis (heel)
- uveitis
- dactylitis
- psoriasis
- Crohn's/colitis
- good response to NSAIDs
- family history for SpA
- HLA-B27
- elevated CRP

n=649 patients with back pain;

Overall

Sensitivity: 82.9%, Specificity: 84.4%

Imaging arm alone

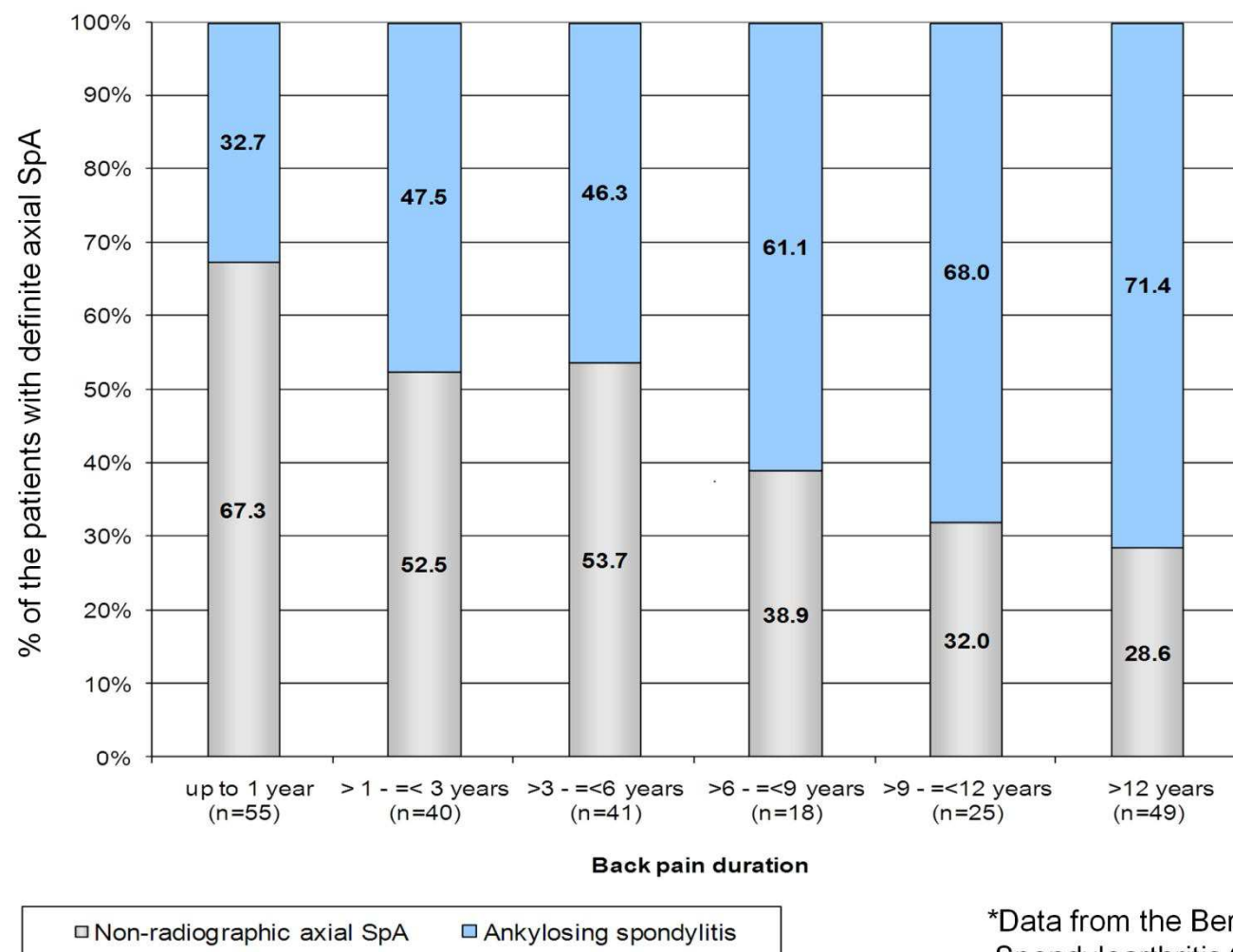
Sensitivity: 66.2%, Specificity: 97.3%

Clinical arm alone

Sensitivity: 56.6%, Specificity: 83.3%



Ratio of Non-radiographic Axial SpA to AS among Patients with Definite Axial SpA in Relation to Symptom Duration at the Time of Diagnosis*



*Data from the Berlin Early Spondyloarthritis Clinic

Progression of Non-radiographic Axial SpA to AS: Data from GESPIC*

Non-radiographic axial SpA



no definite radiographic sacroiliitis (grade 0 at the right side, grade 1 – possible subchondral sclerosis – at the left side)

**12%
in 2 years**

**Main predictor:
elevated CRP****

Ankylosing spondylitis



definite radiographic sacroiliitis (grade 2 bilaterally) fulfilling the radiographic criterion of the modified New York criteria

*GESPIC = GERman Spondyloarthritis Inception Cohort

**Odds ratio for progression in patients with elevated serum C-reactive protein level (>6 mg/l) was: 4.11 (95% CI 1.13-14.95).

Similarities and Differences between Ankylosing Spondylitis (AS) and Non-radiographic Axial SpA (nr-axSpA)

	GESPIC ¹			Herne-Cohort ²	
	All AS	AS ≤5 years	nr-axSpA ≤5 years	AS	nr-axSpA
	N=236	N=119	N=226	N=56	N=44
Age, years	35.6	36.1	36.1	41.2	39.1
HLA-B27 (+), %	82.2	73.1	74.7	89.1	86.4
Female, %	36.0	34.5	57.1 [§]	23.2	68.2*
BASDAI (0-10)	4.0	4.0	3.9	4.3	3.6
Total pain (0-10)	5.0	4.8	4.8	5.0	4.0
BASFI (0-10)	3.1	3.1	2.5 [§]	2.9	1.5
Patient's global (0-10)	5.0	5.0	4.9	4.6	4.0
Abnormal CRP, %	51.9	49.6	29.8 [§]	69.1	29.5*

[§] p < 0.05 vs AS ≤5 years, *p < 0.05 vs AS

1. Rudwaleit M et al. Arthritis Rheum 2009;60:717-27.

2. Kiltz U et al. Arthritis Care Res (Hoboken) 2012;64:1415-22



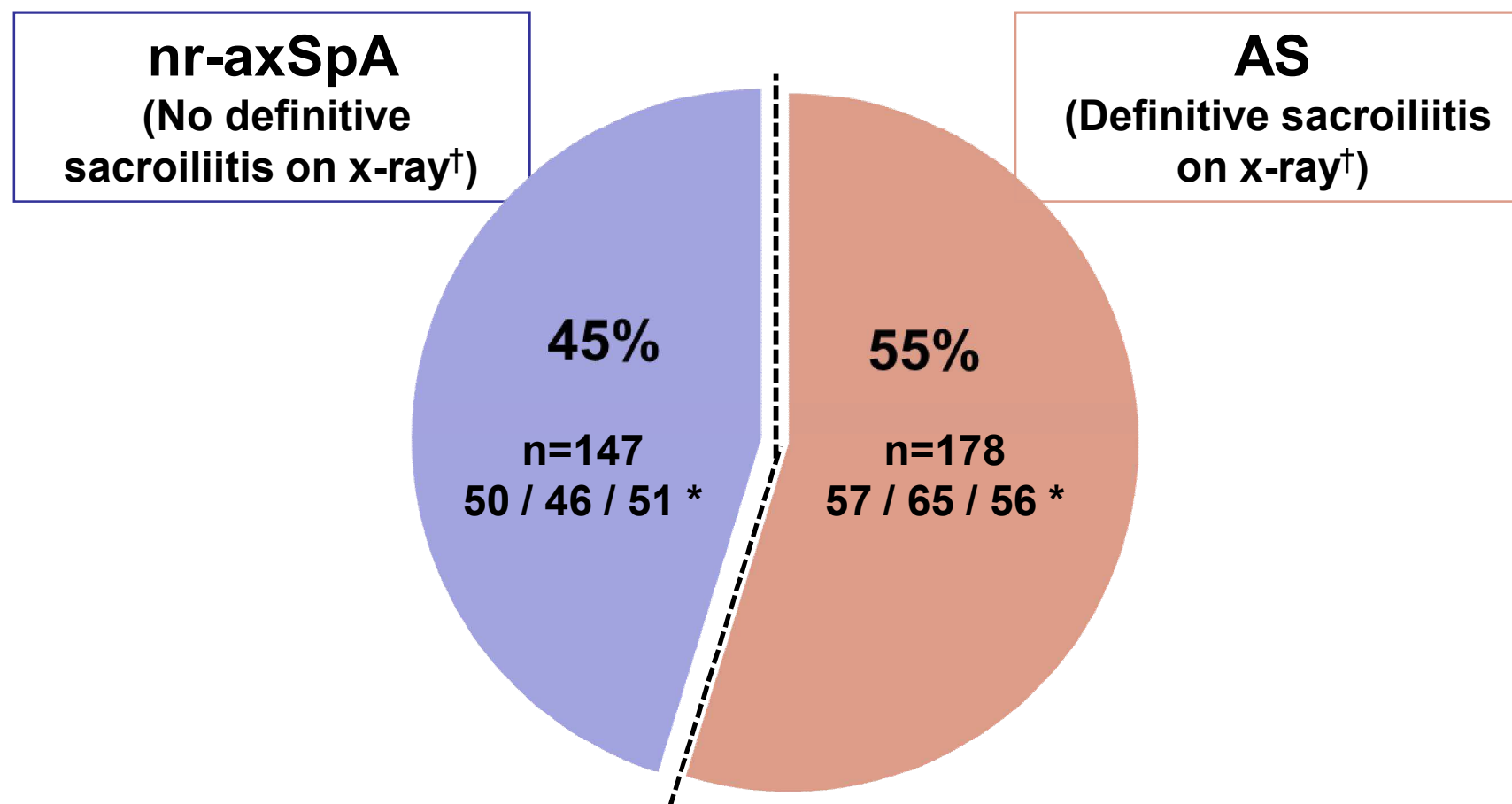
RAPID-axSpA Key Inclusion Criteria

- Patients aged ≥ 18 years, **active axial spondyloarthritis (axSpA)** of ≥ 3 months duration as defined by the ASAS* criteria¹
- The patient population reflected the broad axSpA population, including **both patients with ankylosing spondylitis (AS) and also patients with active axSpA without definitive changes on plain x-ray** (i.e. not meeting the modified new York [mNY] classification criteria). This latter group is denoted as nr-axSpA or non-radiographic axSpA²
 - Randomization was stratified by site, mNY criteria status (meeting criteria yes/no), and prior TNF-antagonist exposure (yes/no)
- **Patients must have:**²
 - Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4
 - Spinal pain ≥ 4 on a 0 to 10 Numerical Rating Scale (NRS)
 - CRP > upper limit of normal (ULN=7.9 mg/L) **or** current evidence for sacroiliitis (ie. within the last 3 months from screening) on magnetic resonance imaging (MRI) as defined by ASAS criteria¹
- **Patients must have failed ≥ 1 NSAID**²

1. Sieper, Ann Rheum Dis, 2009: 68 (Suppl II), ii1-ii44

2. Landewé et al, ACR 2012. Abstract 28889

RAPID-axSpA Trial Population – Recruited Using ASAS Criteria

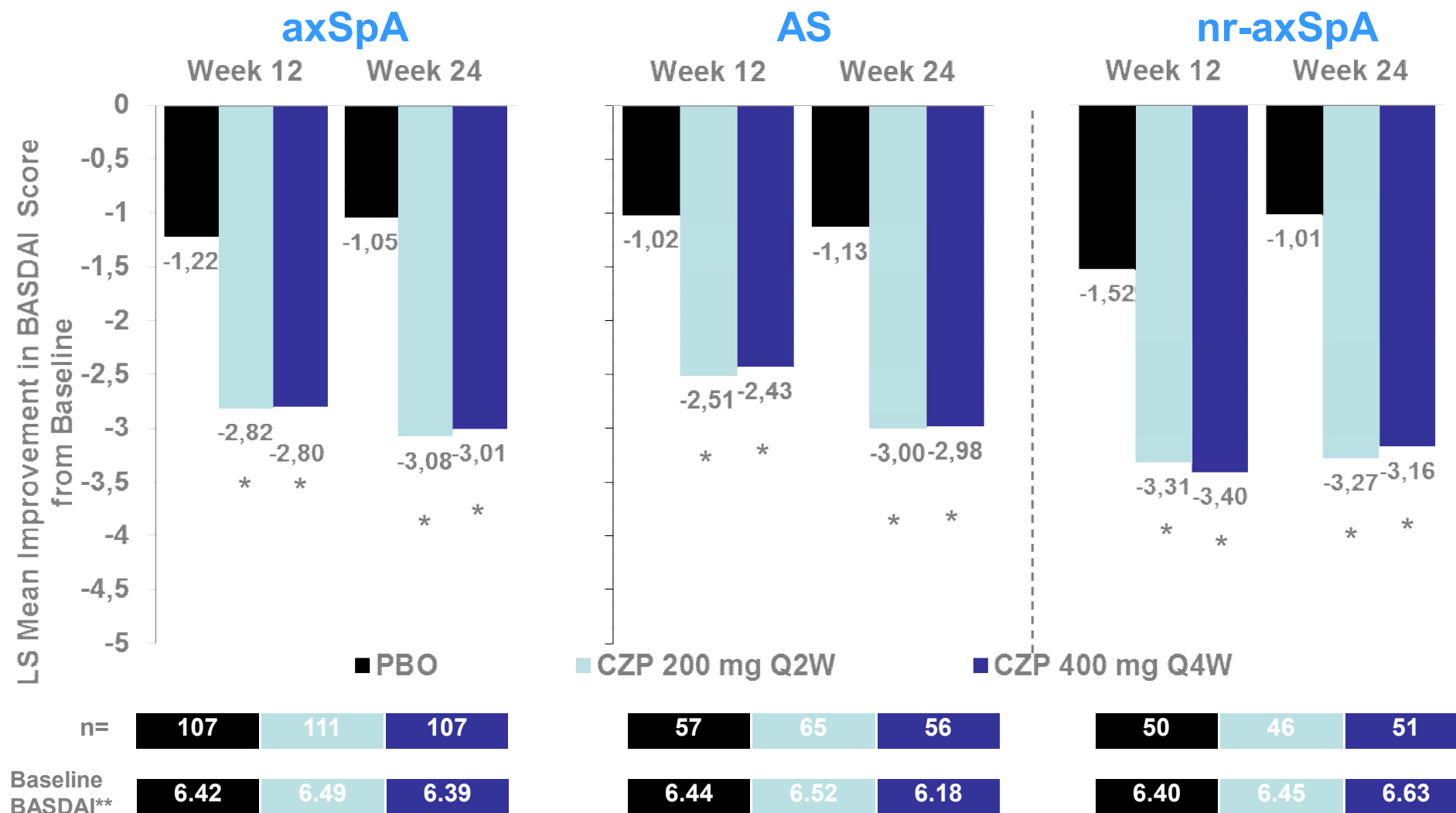


Randomized set (RS)

*PBO / CZP 200 mg Q2W / CZP 400 mg Q4W

†Based on mNY criteria

BASDAI Improvement at Weeks 12 and 24



* $p < 0.001$ CZP vs. PBO, **FAS; LOCF; RS

Landewé et al. ACR 2012. Abstract 28889

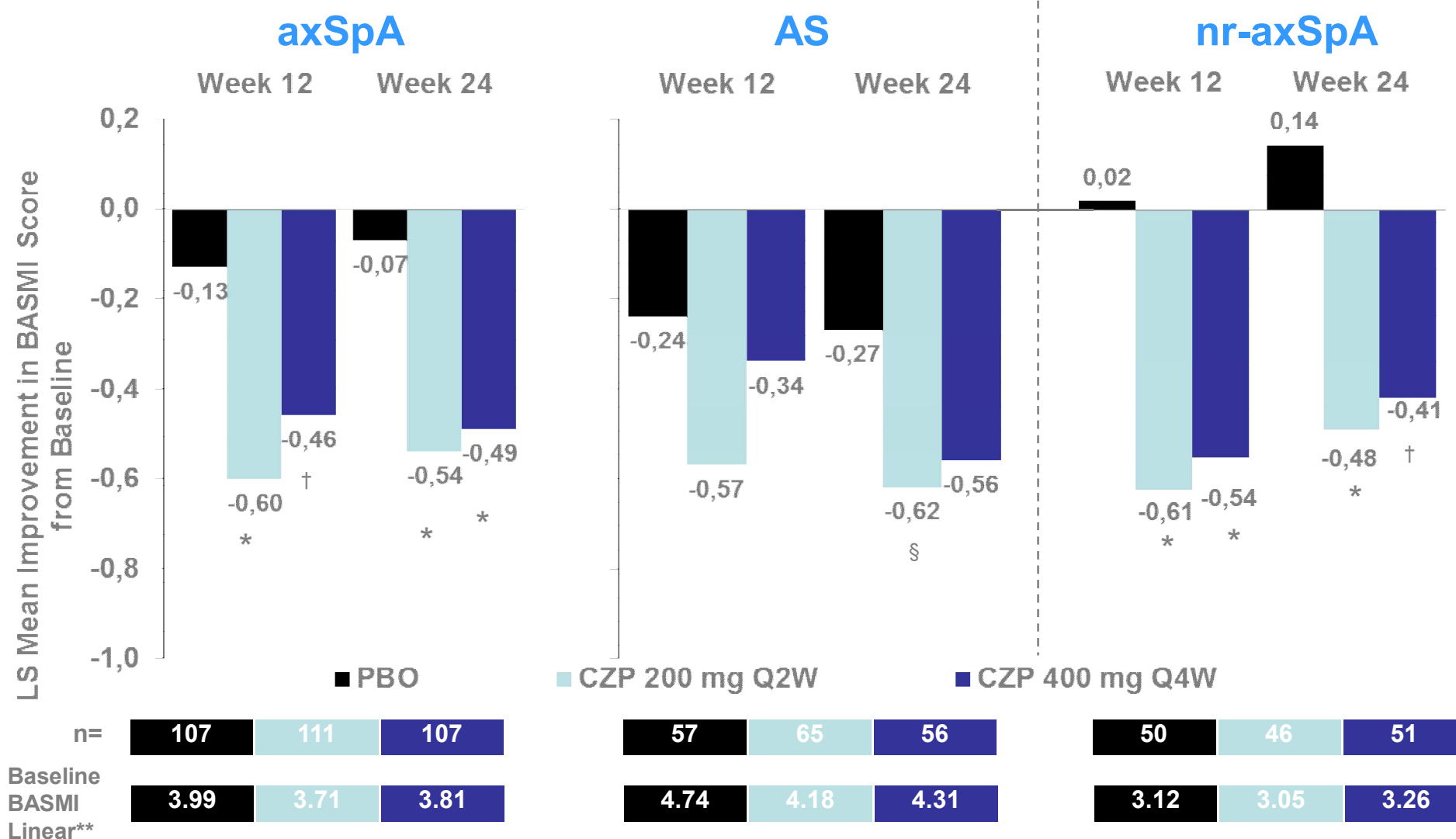
BASFI Improvement at Weeks 12 and 24



* $p < 0.001$; † $p < 0.01$ CZP vs. PBO; ** FAS; LOCF; RS

Landewé et al. ACR 2012. Abstract 28889

BASMI Linear Improvement at Weeks 12 and 24



* $p < 0.001$; † $p < 0.01$; § $p < 0.05$ CZP vs. PBO; **FAS; NRI; RS

ASAS Classification Criteria for Axial Spondyloarthritis (SpA)

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plus
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OR

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- dactylitis
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- good response to NSAIDs
- family history for SpA
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Imaging arm alone

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Clinical arm alone

Sensitivity: 56.6%, Specificity: 83.3%



How to Define Active Inflammatory Lesions (‘positive MRI’) of the Sacroiliac Joint

- The presence of definite subchondral bone marrow edema/osteitis highly suggestive of sacroiliitis is mandatory.
- The presence of synovitis, capsulitis, or enthesitis only without subchondral bone marrow edema/ osteitis is compatible with but not sufficient for making a diagnosis of active sacroiliitis.

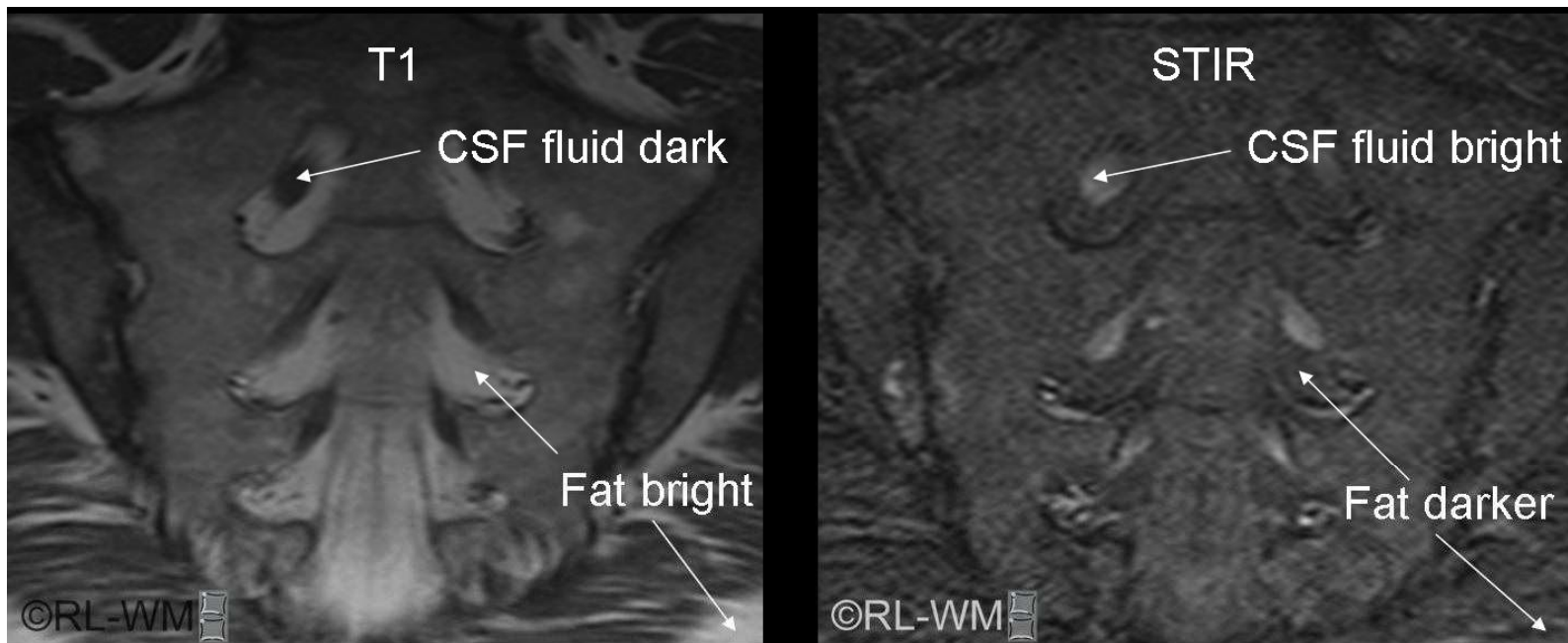
MRI of the SIJ: T1 and STIR sequence

- **T1SE (T1 spin echo) = Fat-sensitive sequence:**
Fat bright, fluid dark
Reference structures: subcutaneous and retroperitoneal fat
- **STIR (Short tau inversion recovery) = Fluid-sensitive sequence:**
Fluid bright, fat dark
Reference structures: blood vessels, CSF, intervertebral disc
- Cortical bone: black on both sequences
- **Contrast-enhanced sequences have not been shown to have an advantage over the STIR sequence alone for clinical practice and should not be used in daily routine¹.**

¹Madsen KB et al. J Rheumatol 2010;37:393

Baraliakos X et al. Ann Rheum Dis 2005;64:1141

MRI of the SIJ: T1 and STIR sequence



T1 : Fat is bright, fluid/edema is dark/lower signal

STIR: Fat is darker, fluid/edema is brighter signal

Can use CSF and fat as reference and to help window the image

Which MRI sequence do you see on this image?



1. T1-weighted

2. STIR

Which MRI sequence do you see on this image?

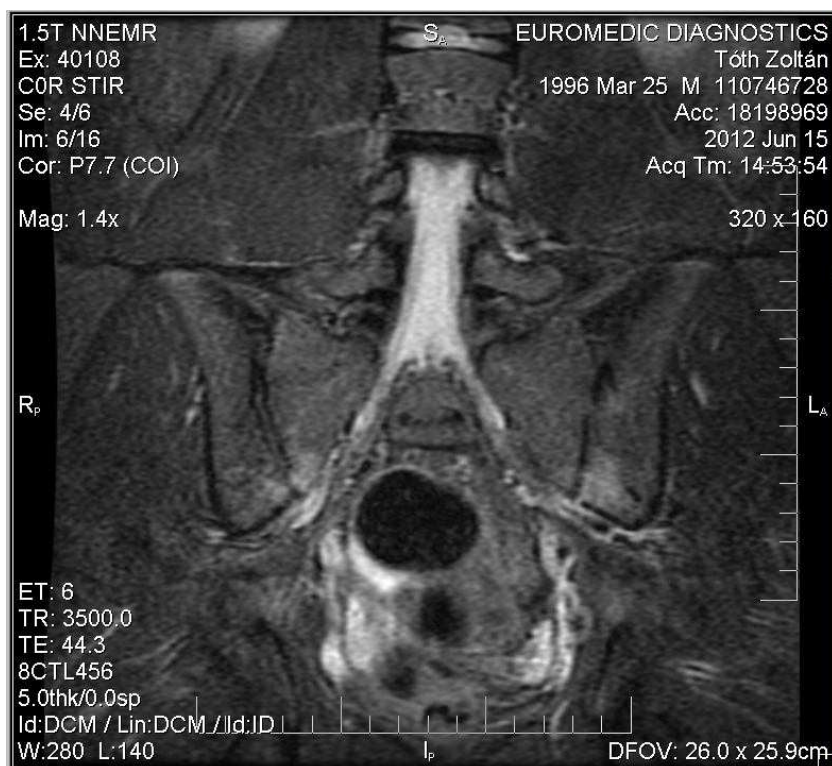


1. T1-weighted

2. STIR

Sequence	Cerebro-spinal fluid	Intervertebral disc	Subcutaneous fat	Active inflammatory laesion
T1-weigted	Hypo-intense (dark)	Hypo-intense (dark)	Hyperintense (bright)	Hypo-intense (dark)
STIR	Hyperintense (bright)	Hyperintense (bright)	Hypo-intense (dark)	Hyperintense (bright)

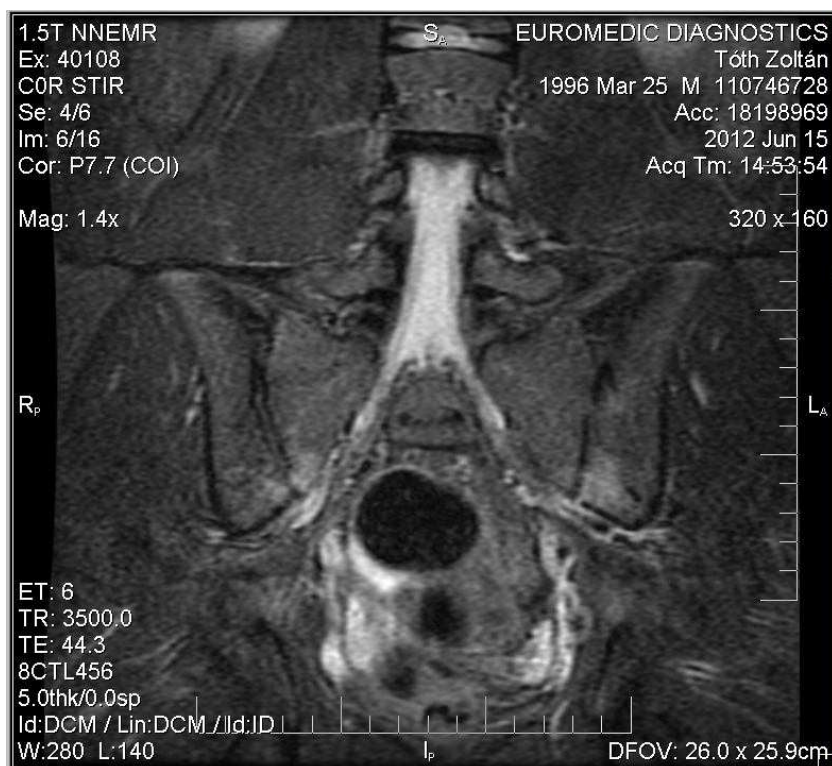
Which MRI sequence do you see on this image?



1. T1-weighted

2. STIR

Which MRI sequence do you see on this image?

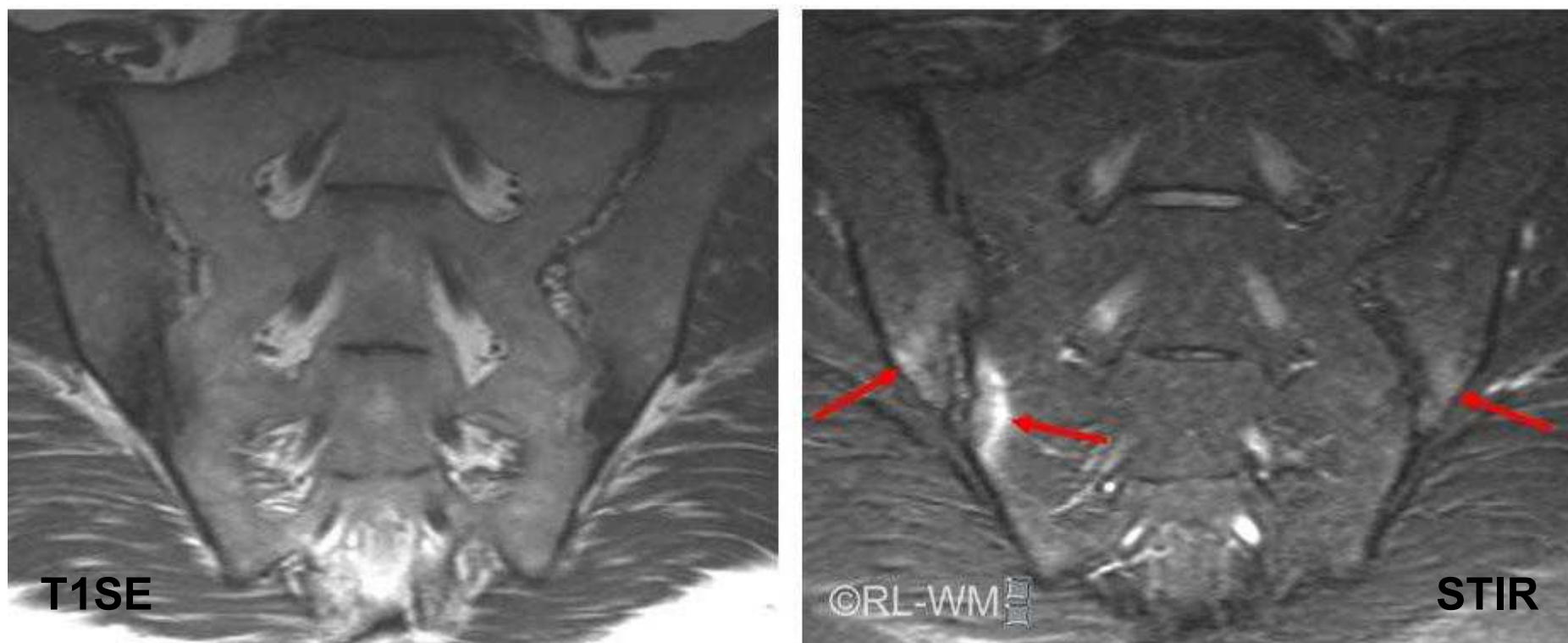


1. T1-weighted

2. STIR

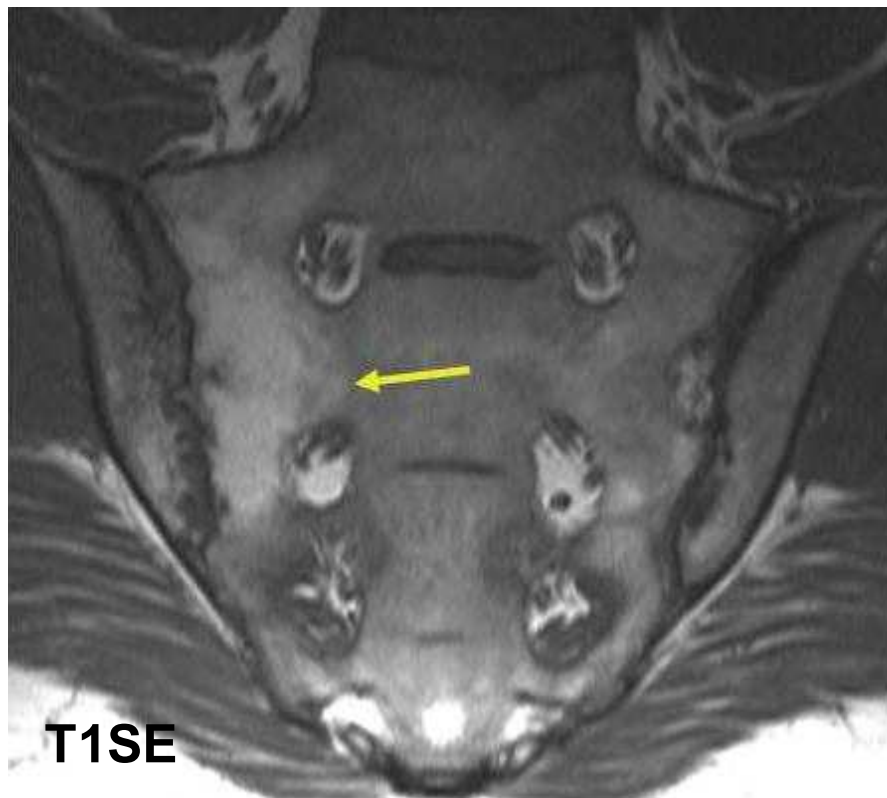
Sequence	Cerebro-spinal fluid	Intervertebral disc	Subcutaneous fat	Active inflammatory laesion
T1-weighted	Hypo-intense (dark)	Hypo-intense (dark)	Hyperintense (bright)	Hypo-intense (dark)
STIR	Hyperintense (bright)	Hyperintense (bright)	Hypo-intense (dark)	Hyperintense (bright)

Abnormalities in SIJ characteristic of SpA: Bone Marrow Edema



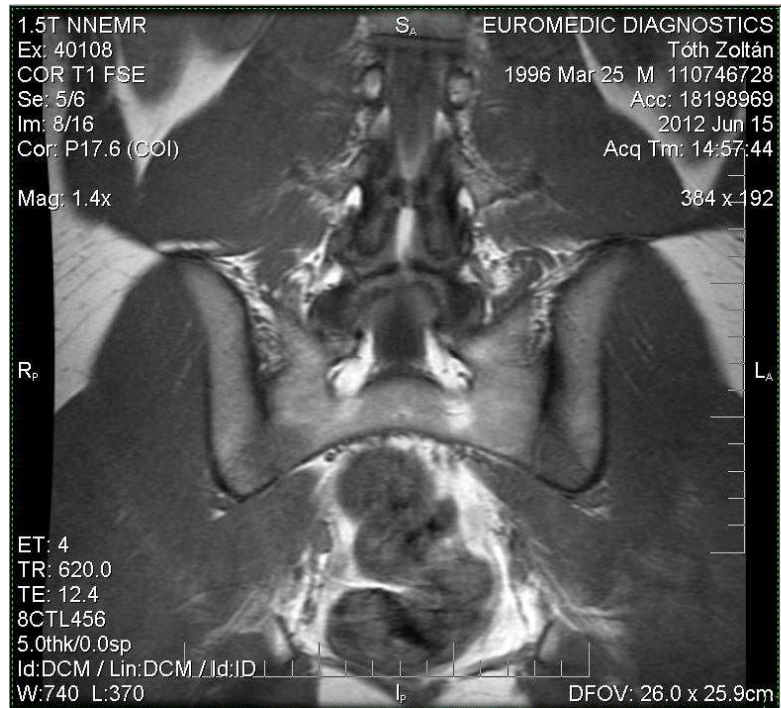
Definition of Bone Marrow Edema (BME): Increase in bone marrow signal in the SIJ on STIR images; the center of the sacrum at the same craniocaudal level is used as the primary reference for normal bone marrow signal

Abnormalities in SIJ characteristic of SpA: Fat Infiltration



Definition of Fat Infiltration: Focal increased signal in bone marrow on T1-weighted images

Can you see any sign of active sacroiliitis?



1. Yes 2. No

Can you see any sign of active sacroiliitis?

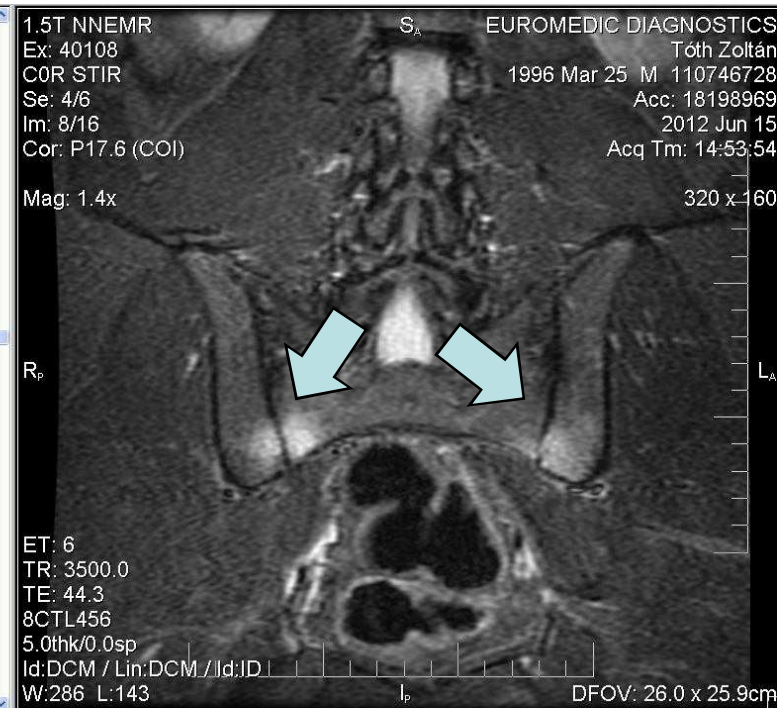
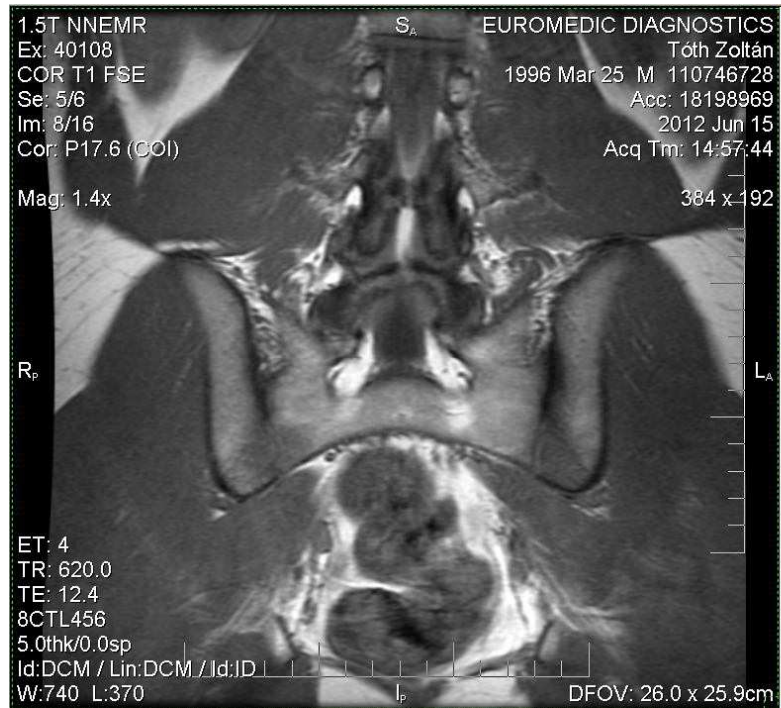


1. Yes 2. No

Sequence	Cerebro-spinal fluid	Intervertebral disc	Subcutaneous fat	Active inflammatory laesion
T1-weighted	Hypo-intense (dark)	Hypo-intense (dark)	Hyperintense (bright)	Hypo-intense (dark)
STIR	Hyperintense (bright)	Hyperintense (bright)	Hypo-intense (dark)	Hyperintense (bright)

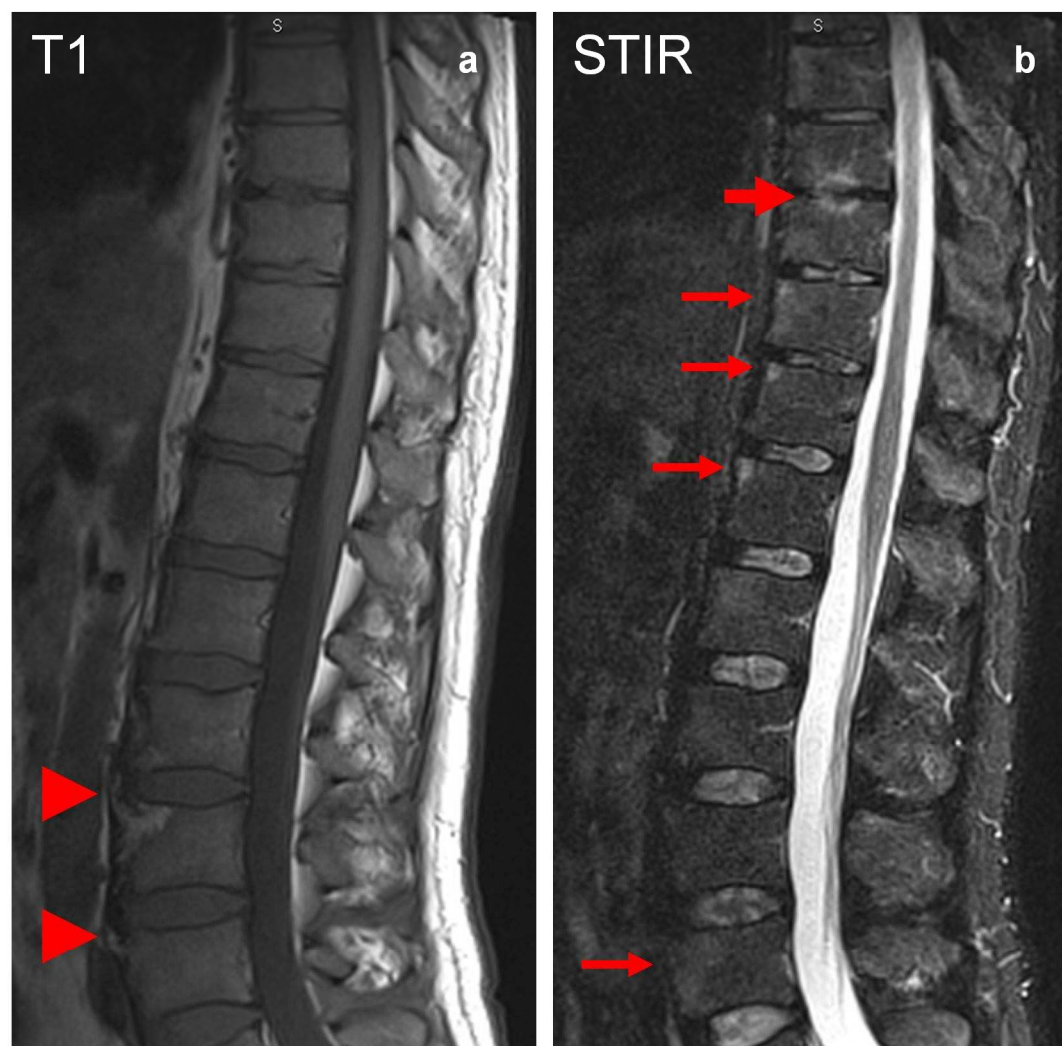
Active Inflammatory Lesions: General Remarks

- Technical aspects:
 - STIR images are usually sufficient to detect active (acute) inflammatory lesions; exception: synovitis (not detectable with STIR only).
- Amount of signal required
 - If there is 1 signal (lesion) only, this should be present on at least 2 slices. If there is more than 1 signal on a single slice, 1 slice may be enough.



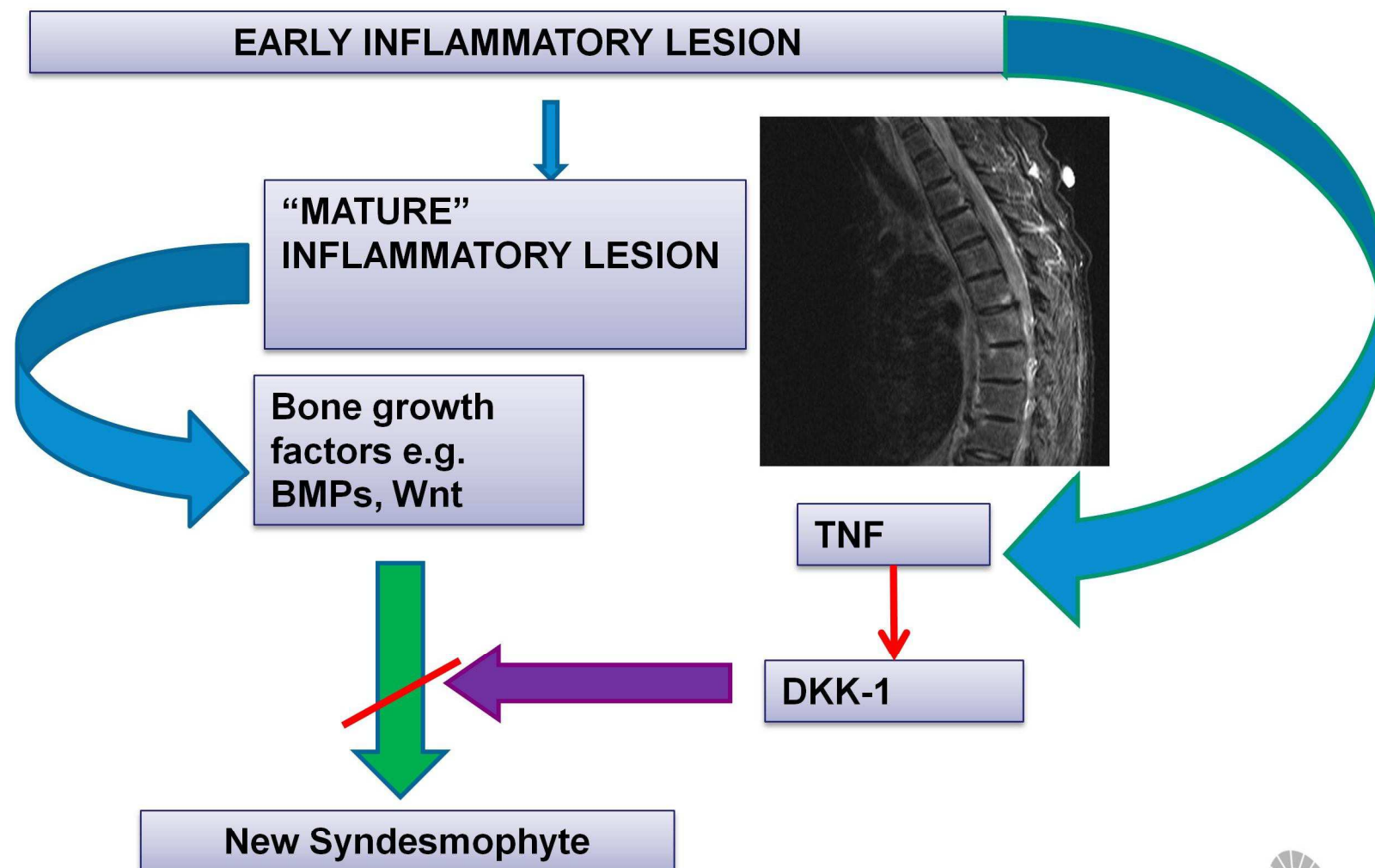
Sequence	Cerebro-spinal fluid	Intervertebral disc	Subcutaneous fat	Active inflammatory laesion
T1-weighted	Hypo-intense (dark)	Hypo-intense (dark)	Hyperintense (bright)	Hypo-intense (dark)
STIR	Hyperintense (bright)	Hyperintense (bright)	Hypo-intense (dark)	Hyperintense (bright)

Active and Chronic Inflammatory Lesions of the Spine in Spondyloarthritis by MRI



Active spondylodiscitis (bold arrow) and **active spondylitis anterior** (thin arrows) in the STIR sequence (**b**) and **fatty degeneration** and **syndesmophytes** (arrow heads) in the T1 sequence (**a**)

Release of the TNF Brake Hypothesis in Ankylosing Spondylitis



The Window of Opportunity for Disease Modification with Anti-Inflammatory Agents

HYPOTHESIS

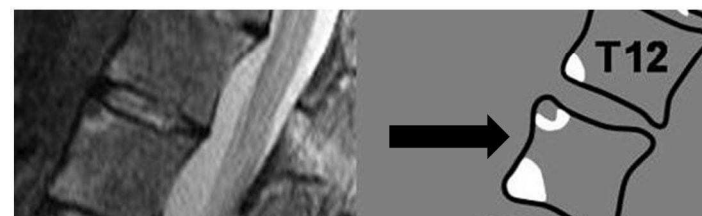
In the individual patient the effect of anti-TNF therapy on radiographic progression depends on the relative number of “acute” and “mature” inflammatory lesions. Early diagnosis is a pre-requisite for advances in disease modification.

“Acute” Lesion



**Complete Resolution with anti-TNF
No reparation/new bone formation**

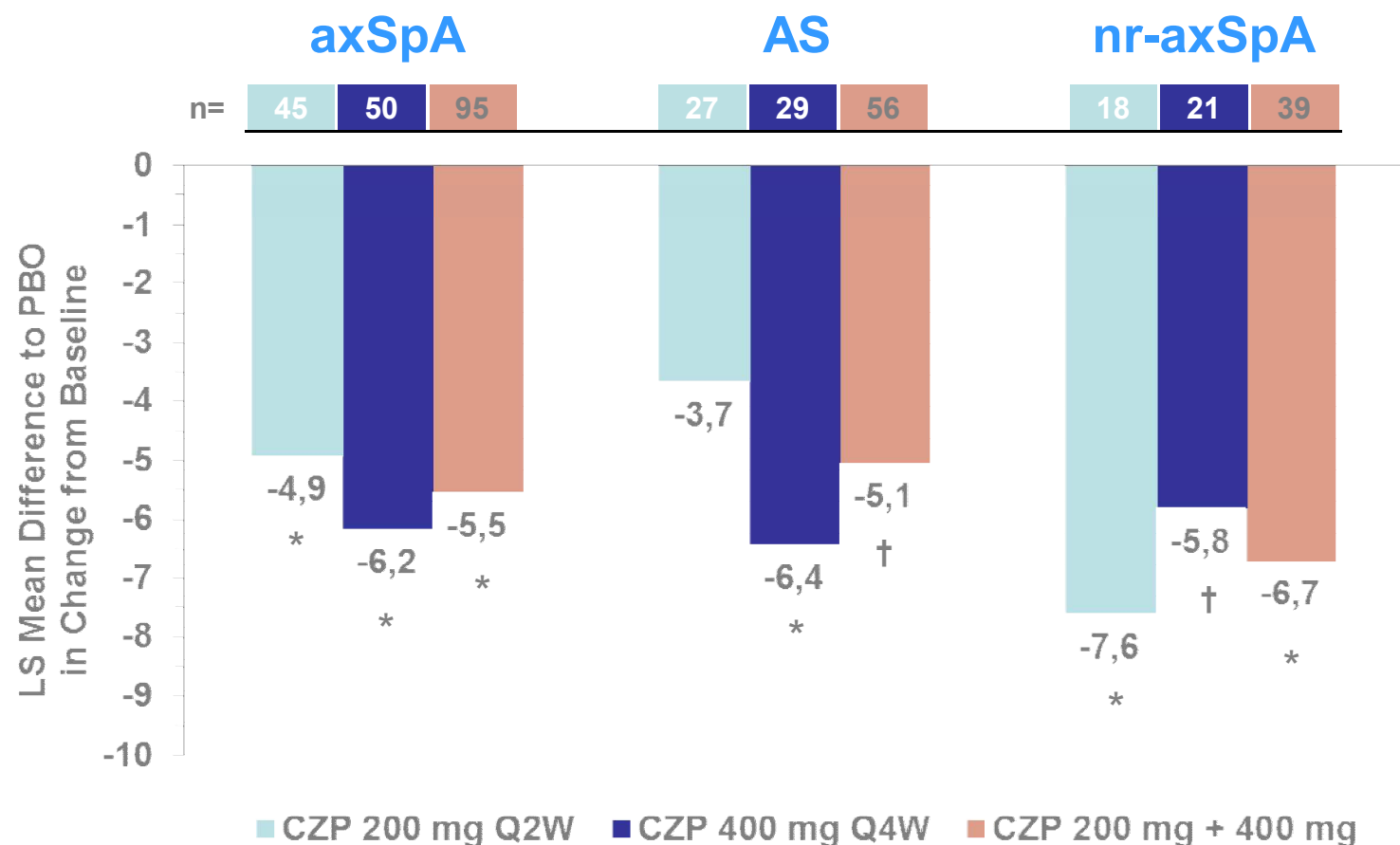
“Mature” Lesion



**Resolution of inflammation by anti-TNF
therapy allows reparation and new bone
formation**

Mean Difference to Placebo in MRI SI Joint SPARCC Scores at Week 12

Baseline SPARCC MRI SIJ scores were comparable between AS and nr-axSpA populations



Greater reductions in SIJ inflammation were observed for patient subgroups with <5 year symptom duration, age <45 years and in males.

* $p \leq 0.001$; † $p < 0.05$ CZP vs. PBO, analysis of covariance. MRI Set MRI carried out using short-tau-inversion recovery sequences.

van der Heijde et al. ACR 2012. Abstract 28913

Summary ...

- ASAS classification criteria is a useful tool for early diagnosis of axial spondyloarthritis
 - MRI of sacroiliac joint and HLA-B27 determination are crucial
- The early and effective treatment of axial spondyloarthritis can slow the radiographic progression of the disease





TÁMOP 4.2.4.A

This research was supported by the European Union and the State of Hungary co-financed by the European Social Fund in the framework of TAMOP-4.2.4.A/2-11/1-2012-0001 'National Excellence Program'.