Imaging of axial spondyloarthritis including ankylosing spondylitis

ACR 2012

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Modified New York Criteria 1984 for Diagnosis/Classification of Ankylosing Spondylitis

- **Clinical Criteria**
  - inflammatory back pain (Calin 1977)
  - reduced spinal mobility in 2 planes ( < 3 cm)
  - reduced thoracic excursion (< 3 cm)

- **Radiologic Criterium**
  - Sacroiliitis ≥ grade II bilat.
  - or > grade II unilat.

> 95% of AS patients have definite changes in the SI joints

van der Linden et al. A&R 1984
# ASAS Classification Criteria for Axial SpA

**in patients with ≥ 3 months chronic back pain and age at onset < 45 years**

<table>
<thead>
<tr>
<th>Sacroiliitis on imaging</th>
<th>HLA-B27</th>
</tr>
</thead>
<tbody>
<tr>
<td>plus</td>
<td>plus</td>
</tr>
<tr>
<td>≥ 1 SpA feature</td>
<td>≥ 2 other SpA features</td>
</tr>
</tbody>
</table>

**SpA features**
- IBP
- arthritis
- enthesitis
- uveitis
- dactylitis
- psoriasis
- Crohn’s/colitis
- Good response to NSAIDs
- Family history for SpA
- HLA-B27
- elevated CRP

**Validation study in 649 patients with back pain**
- Sensitivity 82.9%
- Specificity 84.4%  

**Imaging obligatory**
- Sensitivity 66.2%
- Specificity 97.3%

*Rudwaleit et al. Ann Rheum Dis 2009*
Axial spondyloarthritis including AS

(inflammatory) back pain

Stage 1
Sacroiliitis (MRI)

Stage 2
Radiographic changes due to sacroiliitis (NY criteria)

Stage 3
Radiographic changes due to spondylitis (syndesmophytes)

non-radiographic axSpA

Ankylosing spondylitis
Defining active sacroiliitis and spondylitis on MRI

- a consensual approach by the ASAS/OMERACT MRI group

- Active inflammatory lesions such as bone marrow oedema (BMO)/ osteitis, synovitis, enthesitis and capsulitis associated with SpA can be detected by MRI.
- Among these, the clear presence of bone marrow edema / osteitis was considered essential for defining active sacroiliitis and spondylitis (> 3 lesions).
- Structural damage lesions such as sclerosis, erosions, fat deposition and ankylosis can also be detected by MRI.
- At present, however, the exact place of structural damage lesions for diagnosis and classification is less clear, particularly if these findings are minor.
- The ASAS group approved these proposals by voting.

Extended inflammation in the sacroiliac joints predicts development to AS (MRI and HLA-B27)

- Sensitivity and specificity 77%
- Positive predictive value 60 - 80%
- Negative predictive value > 80%
- No predictive value of bilateral involvement

Does axial SpA always start in the sacroiliac joints?

no, but yes in the majority of cases

50% spinal inflammation in patients with axSpA < 5 years disease duration

5-10% in other studies

The likelihood of a positive MRI of the sacroiliac joints in patients with early IBP (< 2 years duration)

- n = 68 patients
- 38% male
- mean age 35 years
- 46% HLA B27+
- 24% psoriasis
- 15% IBD
- 15% AAU
- 20% structural changes in the SI joints at baseline (n=14)
- 35% positive MRI at baseline (n=24)

Prediction of positive MRI by HLA B27 and male gender
- in MRI-positive patients 88%
- in MRI-negative patients 27%

In an HLA B27- patient with a negative MRI at baseline the likelihood of a positive MRI in the future is < 5%

Chronic changes in the SI joints (MRI)

Rheumatologist training to recognize lesions on T1-weighted MRI enhances diagnostic utility of MRI in patients with ankylosing spondylitis

Maksymowych WP, et al., Arthritis Rheum 2009; 60 S200; #540
Comparison of conventional X-ray with CT using SASSS for AS patients

- CT proved more sensitive in the detection of sclerosis and syndesmophytes (3D-reconstruction)
- no significant difference for erosions and squaring
- higher SASSS-Score using CT in the lumbar spine

Lee S-H, et al., Arthritis Rheum 2009; 60 S198; #534
CT scanning facilitates the diagnosis of sacroiliitis in patients with suspected spondylarthritis: results of a prospective multicenter French cohort study.

METHODS: The Echography in SpA French cohort consists of 489 patients with suspected SpA. Pelvic CT scanning was performed if sacroiliitis on radiography was considered uncertain or if patients presented with buttock pain duration of > 6 months. A set of 100 paired radiographs and CT scans was read in a blinded manner by 2 radiologists. One of them read the 173 available pairs of radiographs and CT scans.

RESULTS: After training, interreader reliability was moderate for sacroiliitis grading on radiographs ($\kappa = 0.59$), excellent on CT scans ($\kappa = 0.91$), and excellent for ascertaining sacroiliitis on both radiographs ($\kappa = 1$) and CT scans ($\kappa = 0.96$). The first and second readers considered the quality of imaging to be excellent in 66% and 67%, respectively, of the radiographs ($\kappa = 0.88$) and in 93% and 92%, respectively, of the CT scans ($\kappa = 0.93$). Concordance between radiographs and CT scans was low for sacroiliitis grading ($\kappa = 0.08$) or ascertainment ($\kappa = 0.16$). Definite sacroiliitis was ascertained on radiographs in 6 patients (3.5%) (confirmed by CT scans in 4 patients) and on CT scans in 32 patients (18.5%). A history of uveitis was associated with definite sacroiliitis on radiographs ($p = 0.04$) and CT scans ($p < 0.0001$).

CONCLUSION: Definite sacroiliitis was underestimated by radiography. CT scanning should facilitate the diagnosis of AS in patients with suspected SpA.

Fat accumulation and syndesmophytes in AS (MRI)

The fatty Romanus lesion (FRL) – a non-inflammatory spinal MRI lesion specific for axial SpA

> 5 FRL have a LR of 12,6 for AS

Benett A et al. Arthritis Rheum 2009; 60 S195; #526
Spinal inflammation lesions as detected by MRI in patients with early AS are more often observed in posterior spinal structures.

Patients with SpA and a short history of IBP (n = 11) had significantly more lesions in posterior spinal structures than in vertebral bodies: 90.9 vs 27.2%, respectively (P < 0.003). Isolated changes in posterior spinal structures were seen in 8 of these patients (72.7%).

Does the site of MRI abnormalities match the site of recent-onset inflammatory back pain (IBP)? The DESIR cohort.

OBJECTIVES: To assess whether the site of axial pain (thoracic spine, lumbar spine or buttock(s)) was associated with the site of MRI lesions in patients with recent IBP.

METHODS: Cross-sectional study with 708 patients with possible SpA. Radiographs of the sacroiliac joints (SIJs) and MRI scans of the SIJs and thoracic and lumbar spine were obtained routinely. Associations between pain sites and sites of inflammatory and structural MRI changes were evaluated using separate multivariate logistic regressions.

RESULTS: Of the 648 patients with complete data, 61% had thoracic pain, 91.6% lumbar pain and 79.2% buttock pain. MRI inflammation was seen in 19%, 21% and 46% of patients at the thoracic, lumbar and SIJ sites, respectively. By multivariate analysis, pain was significantly associated with MRI inflammation only at the same site (adjusted OR (aOR) (thoracic) (pain) 1.71; 95% CI 1.09 to 2.67; p=0.02; aOR (lumbar pain) 2.53; 95% CI 1.03 to 6.20; p=0.04; aOR (buttock pain) 2.86; 95% CI 1.84 to 4.46; p<0.0001).

Pain site was not significantly associated with the site of structural MRI changes, except for buttock pain and SIJ structural MRI changes (aOR (buttock pain) 1.89; 95% CI 1.22 to 2.90; p=0.004). The association between pain site and site of MRI inflammation persisted in the subgroups with normal or doubtful SIJ radiographs or with ASAS criteria for axSpA.

CONCLUSIONS: The site of pain (thoracic spine, lumbar spine or buttock(s)) is associated with MRI inflammation at the same site in patients with recent IBP.

Prognostic factors in AS (SpA)

- no agreement on 'severity' (ASAS discussion)
- gender (male patients have more structural changes)
- x-rays (presence of one syndesmophyte predicts development of future syndesmopyhtes)
- degree of inflammatory sacroiliac lesions (MRI)
- elevated CRP
- smoking
- manual work
- hip involvement
- cervical spine involvement
- peripheral arthritis
Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS)

0  NORMAL
1  EROSIONS
1  SCLEROSIS
1  SQUARING
2  OBVIOUS
2  SYNDSEMPHOPHYES
3  TOTAL BONY
3  BRIDGES

(range 0-72)

Radiographic progression of AS patients treated with celecoxib or another NSAID continuously or on demand

- 70% of patients treated with celecoxib
- mean difference of dose < 50 mg/day

Continuous NSAID use reverts the effects of inflammation on new bone formation in patients with ankylosing spondylitis

The effect of CRP values

Objectives

- Determine whether infliximab (IFX)+naproxen (NPX) therapy is superior to NPX monotherapy in patients with active, moderate to severe axial SpA who were naïve to NSAIDs or had a submaximal dose of NSAIDs.
  - Improvement of signs, symptoms, and function
  - Reduction of active MRI inflammation of the spine and SI joints
- Part I analysis: Evaluate efficacy in each treatment group.
- Part II analysis: In patients who achieved ASAS partial remission in Part I, measure changes in response during follow-up with either NPX or no treatment.

ASAS=Assessment in Ankylosing Spondylitis; SI=sacroiliac.
INFAST Study Design

**Part I: Treatment Phase**
- 2:1 randomization
- IV infusions: weeks 0, 2, 6, 12, 18, and 24

**Part II: Follow-up Phase**
- Only patients with ASAS partial remission at week 28
- Discontinue IFX
- 1:1 randomization

IFX (5 mg/kg) + NPX (1000 mg/d)

PBO + NPX (1000 mg/d)

NPX (1000 mg/d)

No Treatment

Patients without ASAS partial remission discontinue study

Screening/Washout

Week 28

MRI

Week 52

MRI at Week 52 or ET

ET=early termination; IFX=infliximab; IV=intravenous; NPX=Naproxen; PBO=placebo.
Key Patient Inclusion Criteria

- 18 – 48 years of age
- NSAID-naïve or submaximal dose of NSAIDs
- Axial SpA according to ASAS classification criteria with symptom duration < 3 years
- Signs of active sacroiliitis on MRI
- Active disease at screening and baseline, defined as
  - total back pain evaluation of ≥ 40 mm
  - BASDAI score of ≥40 mm (on VAS scales of 0 to 100 mm)

BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; VAS=visual analog scale.
# Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IFX+NPX (N=105)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PBO+NPX (N=51)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male</td>
<td>69%</td>
<td>78%</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>31.7 (8.51)</td>
<td>30.7 (7.34)</td>
</tr>
<tr>
<td>Years since symptom onset, mean (SD)</td>
<td>1.76 (0.896)</td>
<td>1.91 (1.439)</td>
</tr>
<tr>
<td>Number of SpA manifestations (SD)</td>
<td>3.8 (1.4)</td>
<td>4.0 (1.23)</td>
</tr>
<tr>
<td>Patients with readable MRIs and active lesions at screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>59%</td>
<td>59%</td>
</tr>
<tr>
<td>SI joint</td>
<td>88%</td>
<td>90%</td>
</tr>
<tr>
<td>Spine or SI joint</td>
<td>91%</td>
<td>94%</td>
</tr>
<tr>
<td>SI x-ray findings (bilateral ≥grade 2 or unilateral ≥grade 3), n (%)</td>
<td>61 (57.5)</td>
<td>33 (63.5)</td>
</tr>
<tr>
<td>BASDAI (100-mm VAS), mean (SD)</td>
<td>64.4 (15.37)</td>
<td>63.0 (15.43)</td>
</tr>
<tr>
<td>HLA-B27–positive status, n (%)</td>
<td>87 (82.1)</td>
<td>47 (90.4)</td>
</tr>
<tr>
<td>BASFI (100-mm VAS), mean (SD)</td>
<td>53.1 (21.92)</td>
<td>54.0 (22.26)</td>
</tr>
</tbody>
</table>

BASFI=Bath Ankylosing Spondylitis Functional Index; HLA=human leukocyte antigen.

<sup>a</sup>For disease characteristics, N=106. <sup>b</sup>For disease characteristics, N=52.
Percentage of Patients with ASAS Partial Remission in Part I

Patients With ASAS Partial Remission, %

- **Week 2**
  - IFX+N PX (N=105) 28.6%
  - PBO+N PX (N=51) 11.8%
  - P = 0.0251

- **Week 6**
  - IFX+N PX (N=105) 41.0%
  - PBO+N PX (N=51) 15.7%
  - P = 0.0018

- **Week 18**
  - IFX+N PX (N=105) 51.4%
  - PBO+N PX (N=51) 25.5%
  - P = 0.0032

- **Week 28/ET**
  - IFX+N PX (N=105) 61.9%
  - PBO+N PX (N=51) 35.3%
  - P = 0.0021

Primary endpoint
Clinical and MRI Outcomes in Part I

Clinical Outcomes from Baseline to Week 28

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>IFX+NPX (N=105)</th>
<th>PBO+NPX (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline, mean</td>
<td>Week 28, mean</td>
</tr>
<tr>
<td>BASDAI (100-mm VAS)</td>
<td>64.4</td>
<td>18.0</td>
</tr>
<tr>
<td>BASFI (100-mm VAS)</td>
<td>53.1</td>
<td>17.1</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>2.02</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Berlin MRI Scores from Baseline to Week 28

<table>
<thead>
<tr>
<th>MRI Outcome</th>
<th>IFX+NPX (N=105)</th>
<th>PBO+NPX (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Spine score</td>
<td>98</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Baseline, mean</td>
<td>Baseline, mean</td>
</tr>
<tr>
<td></td>
<td>2.9</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>Week 28, mean</td>
<td>Week 28, mean</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>SI joint score</td>
<td>97</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>5.6</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td>1.3</td>
<td>3.0</td>
</tr>
</tbody>
</table>

CRP=C-reactive protein.
Percentage of Patients With Complete Absence of MRI Lesions at Week 28

Patients With Complete Absence of MRI Lesions, %

<table>
<thead>
<tr>
<th>Location of Lesion</th>
<th>IFX+NPX (N=105)</th>
<th>PBO+NPX (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine</td>
<td>60.0</td>
<td>45.1</td>
</tr>
<tr>
<td>SI Joints</td>
<td>27.6</td>
<td>5.9</td>
</tr>
<tr>
<td>Spine+SI Joints</td>
<td>18.1</td>
<td>0</td>
</tr>
</tbody>
</table>

*p = 0.09
*p = 0.0013
*p = 0.0004
### Presence/Absence of Inflammation in Patients with ASAS Partial Remission at Week 28

<table>
<thead>
<tr>
<th>Inflammation on MRI</th>
<th>Patients with ASAS Partial Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFX+NPX (n=63) n (%)</td>
</tr>
<tr>
<td>Absent</td>
<td>20 (31.7)</td>
</tr>
<tr>
<td>Present</td>
<td>43 (68.3)</td>
</tr>
</tbody>
</table>
Patients Enrolled in Part II Follow-up Study (Week 28–52)

- Patients were eligible for Part II if they achieved ASAS partial remission at Week 28.

<table>
<thead>
<tr>
<th>Clinical Status at Week 28</th>
<th>NPX (N=41)</th>
<th>No Treatment (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASDAI (100 mm VAS), mean (SD)</td>
<td>7.1 (6.63)</td>
<td>6.2 (6.99)</td>
</tr>
<tr>
<td>BASFI (100 mm VAS), mean (SD)</td>
<td>5.7 (6.03)</td>
<td>7.1 (10.01)</td>
</tr>
<tr>
<td>CRP (mg/dL), mean (SD)</td>
<td>0.39 (0.786)</td>
<td>0.58 (0.747)</td>
</tr>
<tr>
<td>No MRI inflammation, n/N (%)</td>
<td>11/36 (30.6)</td>
<td>12/37 (32.4)</td>
</tr>
</tbody>
</table>

- In each of the randomized treatment groups in the ITT population in Part II:
  - 31 patients were from the IFX+NPX group in Part I
  - 9 patients were from the PBO+NPX group in Part I

ITT=intent-to-treat.

aN=patients with spine and SI joint MRI scores at Week 28.
ASAS Partial Remission During Part II

$p > 0.1$, for all comparisons

- **Week 34**: NPX (N=40) - 80.0%, No Treatment (N=40) - 65.0%
- **Week 40**: NPX (N=40) - 67.5%, No Treatment (N=40) - 47.5%
- **Week 46**: NPX (N=40) - 57.5%, No Treatment (N=40) - 42.5%
- **Week 52/ET**: NPX (N=40) - 47.5%, No Treatment (N=40) - 40.0%
Percentage of Patients With Complete Absence of MRI Lesions at Week 52

**Spine**
- NPX (N=40): 50.0%
- No Treatment (N=40): 40.0%

**SI Joints**
- NPX (N=40): 7.5%
- No Treatment (N=40): 10.0%

**Spine + SI Joints**
- NPX (N=40): 2.5%
- No Treatment (N=40): 2.5%

*p > 0.05, all comparisons*
Change in Berlin MRI Scores in Part I and Part II for Patients Enrolled in Part II

IFX+NPX → NPX (N=31)
IFX+NPX → No Tx (N=31)
PBO+NPX → NPX (N=9)
PBO+NPX → No Tx (N=9)

Worsening

Part I
Part I
Part I
Part I

Part II
Part II
Part II
Part II

-5.25
-4.50
0
-4.50

Change in Median Berlin MRI SI Joint Score

Part I
Part I
Part I
Part I

5
4
3
2
1
0
-1
-2
-3
-4
-5
-6

Tx=treatment.

aChange in Part I is the difference between the medians at baseline and Week 28. Change in Part II is the difference between the medians at Weeks 28 and 52.
Conclusions

- In Part I, patients with early, active, moderate to severe axial SpA who were treated with IFX+NPX had greater MRI improvement, and a greater percentage achieved MRI remission than patients treated with NPX alone.
- In Part II, no differences were observed in MRI measures for patients who received NPX vs no treatment.
  - Efficacy results from Part II should be interpreted with caution because of the small number of patients.
- The safety profile for IFX+NPX was consistent with that of other anti-TNF biologics.
Radiographic progression in AS patients after 2 years of anti-TNF therapy in comparison to a historical cohort (OASIS)

Radiographic progression after 4 years of anti-TNF - results from GO-RAISE

Mean mSASSS change

% patients with progression > 2 mSASSS units

Braun J, ACR 2011; 423
Longterm structural effect of anti-TNF therapy with infliximab in patients with AS

Although the patient numbers are relatively low and the nature of the historical cohort, we see no evidence for increased radiographic progression under continuous IFX.

In contrast, it seems possible that long-term anti-TNF therapy may even delay the progression of radiographic damage (new bone formation).
Clinical Efficacy and Safety of Continuous anti-TNF Therapy over a Decade in Patients with AS

- n=69 (n=42 at 5yrs, n=29 at 10yrs)
- IFX 5mg/kg q6w

Disease status according to ASDAS

No indication of a loss of efficacy.

The most frequent reason for treatment discontinuation were AEs and pragmatic reasons.

Lack of efficacy and infusion reactions contributed to only 15% of all drop outs (<10% of patients).

Baraliakos et al. [poster]. EULAR 2012 THU0286.
At the end of EASIC: 78% pts had no arthritis and 85% no enthesitis.
<table>
<thead>
<tr>
<th>Baseline parameter (n=73 pat.)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean±SD</td>
<td>40.5±10.5</td>
</tr>
<tr>
<td>BASDAI (0-10 units), mean±SD</td>
<td>6.5±1.4</td>
</tr>
<tr>
<td>BASFI (0-10 units), mean±SD</td>
<td>5.9±1.6</td>
</tr>
<tr>
<td>BASMI (0-10 units), mean±SD</td>
<td>4.1±1.7</td>
</tr>
<tr>
<td>CRP (mg/dl), mean±SD</td>
<td>2.9±2.3</td>
</tr>
<tr>
<td>Disease duration (years), mean±SD</td>
<td>10±8.4</td>
</tr>
<tr>
<td>HLA B27+ (%)</td>
<td>61 (83.6%)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>63 (86.3%)</td>
</tr>
</tbody>
</table>
EASIC imaging substudy – Baseline characteristics

$n$ VEs at baseline

- All VEs: 1526
- VEs without syndesmophytes: 1437

94.2%

Baralaikos X et al. EULAR 2012
Course of different spinal lesions in EASIC

% VE-edges

- INF: Baseline 18.6%, 2 years 1.4%
- FD: Baseline 23.7%, 2 years 32.7%
- Syn: Baseline 5.3%, 2 years 7.7%

Baraliakos X et al. EULAR 2012
Development of new syndesmophytes in relation to the MRI finding at baseline before the start of anti-TNF therapy

Baraliakos X et al. EULAR 2012
Development of new syndesmophytes in relation to the MRI finding at baseline before the start of anti-TNF therapy

Baseline  Anti-TNF therapy  2 years  Relative Risk  5 years

Type 1: INF  71%  INF -  0.8  Synd+

Type 2: FD  29%  FD +  1.5  Synd+

Type 3: INF+ and FD+  3.3

Type 4: INF- and FD-  2.4

no INF, no FD at BL and 2y, no Synd = 1

Baraliakos X et al. ACR 2012
Thank you very much!