Non-Radiographic Axial Spondyloarthritis: A Clinical Perspective

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History of Axial Spondyloarthritis (axSpA)

• Ankylosing Spondylitis

• Widening Criteria to include broader SpA presentations

• Development of ASAS criteria for axSpA
  – Clinical Arm
  – Imaging Arm

• So what is non-radiographic axial spondyloarthritis?
History of axSpA: Modified NY Criteria for AS

• **Clinical criteria:**
  - **Low back pain and stiffness for >3 months**, which improves with exercise but is not relieved by rest
  - **Limitation of motion of the lumbar spine** in both the sagittal and frontal planes
  - **Limitation of chest expansion** relative to normal values correlated for age and sex

• **Radiographic criterion:**
  - **Sacroiliitis** (grade ≥2 bilaterally or grade 3–4 unilaterally)

**Definite AS = radiographic criterion present + ≥1 clinical criterion**

**Probable AS = 3 clinical criteria present or radiologic criterion present without clinical criteria**
So what is missing?

• Other associated symptoms

• Axial disease *without* definite sacroiliitis

• New imaging options
  – CT
  – MRI
Expanding the universe of AS

Pre-Radiographic Stage
(Axial Undifferentiated SpA)

Back Pain

Radiographic Stage

Modified New York Criteria (1984)

Back Pain
Radiographic Sacroiliitis

Back Pain Syndesmophytes

Time (years)

Expanding the universe of AS - Axial SpA

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

- Sacroiliitis on imaging* plus ≥1 SpA feature†
- HLA-B27 plus ≥2 other SpA features#

†SpA features
- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's/colicitis
- Good response to NSAIDs
- Family history for SpA
- HLA-B27
- Elevated CRP.

*Sacroiliitis on imaging
- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA definite radiographic sacroiliitis according to mod NY criteria.

ASAS Axial SpA Criteria are Highly Sensitive and Specific

Gold standard = expert physician's diagnosis

694 patients with onset of chronic low back pain (≥3 months) prior to age 45

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASAS Criteria for Axial SpA</td>
<td>82.9</td>
<td>84.4</td>
</tr>
<tr>
<td>Amor Criteria</td>
<td>69.3</td>
<td>77.9</td>
</tr>
<tr>
<td>Modified Amor Criteria*</td>
<td>82.9</td>
<td>77.5</td>
</tr>
<tr>
<td>ESSG Criteria</td>
<td>72.4</td>
<td>66.3</td>
</tr>
<tr>
<td>Modified ESSG Criteria*</td>
<td>85.1</td>
<td>65.1</td>
</tr>
</tbody>
</table>

* Modified with MRI

Clinical utility of ASAS criteria for Axial SpA

- Relative to gold standard of rheumatologist diagnosis:
  - Imaging arm had specificity 97%, sensitivity 63%
  - Clinical arm had specificity 83%, sensitivity 85%
  - Combined specificity 84%, sensitivity 83%

So what is “non-radiographic Axial SpA”?

• Meets ASAS criteria for AxSpA

• Does not meet mNY criteria for AS

• AxSpa then becomes:
  – “radiographic AxSpA” - or AS
  – “non-radiographic AxSpA”

• Are they different diseases?
Following the flow of Axial SpA

Current terminology used in the US:
- Undifferentiated SpA
- Early AS
- Clinical AS / AS-like disease
- Pre-radiographic AS

SPEED Study

Retrospective cohort study

- Patient chart data 1/85-8/11
- Individuals (N=816) aged 18-44 with chronic low back pain of at least 3 months duration identified as at-risk group

Data collection

- 101 Rheumatologists randomly selected from Census regions (Northwest, Midwest, West and South) to ensure geographic representation
- Rheumatologists randomly selected ~10 currently treated at-risk patients

Prevalence calculation

- Chart data screened against ASAS criteria to establish the proportion of patients with axial SpA
- After post-stratification weighting, proportions were applied to US census data to obtain an estimate of prevalence

Results: Based on ASAS criteria

N = 816 (100%)
18-44 yr old patients diagnosed with chronic back pain for at least 3 months

N = 302 (37%)
Not classified as Axial SpA

N = 514 (63%)
Classified as Axial SpA

Prevalence estimate
- Axial SpA: 0.70% [95%CI 0.38-1.1%]
- Nr-axSpA: 0.35% [95%CI 0.18-0.55%]
- AS: 0.35% [95%CI 0.18-0.55%]

N = 256 (31%)
Classified as AS only

N = 258 (32%)
Classified as nr-axSpA only

**NHANES 2010: AxSpA Prevalence**

**Objective:** Estimate U.S. prevalence of AxSpA by Amor and ESSG criteria

**Methods:** NHANES survey of representative sample of U.S. adults ages 20-69, AS data based on reported diagnosis of AS (no x-rays available)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>% Males</th>
<th>% Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall AS</td>
<td>5103</td>
<td>28</td>
<td>0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall AxSpA</td>
<td>5103</td>
<td>43</td>
<td>0.9</td>
<td>0.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Amor Def/Prob</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall AxSpA</td>
<td>5103</td>
<td>70</td>
<td>1.4</td>
<td>1.1</td>
<td>1.7</td>
</tr>
<tr>
<td>ESSG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HLA-B27 overall prevalence 6.1% and equigender.

Prevalence of AxSpA may be 2-3X estimated prevalence of AS in U.S.
Can new classification improve speed of diagnosis?
Improving the diagnostic delay in axSpA

- 680 patients diagnosed with axSpA surveyed in 2016
  - Data collected included: date of first sx, date of dx, disease characteristics, visits prior to diagnosis, socio-demographic data
  - Diagnostic delay overall and before/after the 2009 introduction of ESPeranza:
    - Program of the Spanish Rheumatology Society for creation of 29 ECUs for diagnosis and F/U of early SpA
      - Outreach from each ECU to PCPs in their area
      - Training 1663 physicians
      - Web platform Results
    - 53% female; 77.1% HLA-B27
    - Mean age at first symptoms 24.4 years
    - Mean age at diagnosis 32.9 years

<table>
<thead>
<tr>
<th>Year of 1st symptoms</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2008</td>
<td>9.48 ± 7.79</td>
</tr>
<tr>
<td>≥2009</td>
<td>2.52 ± 2.07</td>
</tr>
</tbody>
</table>

An outreach strategy can improve early recognition of axSpA
A Possible 2-Step Referral Strategy

Primary care setting

Chronic back pain starting at the age of < 45 years

Ask 3 questions

Buttock pain ?
Improvement by movement ?
Psoriasis ?

If ≥2 positive → Referral to rheumatologist
If < 2 positive → Determine HLA B27
If HLA B27+ → Referral to rheumatologist

Re-analysis and modelling of the study data based on inclusion of HLA-B27


Sensitivity 80.4%
Specificity 75.4%
Possible Screening Approach for Axial SpA Among Patients with Chronic Low Back Pain

- Chronic Back Pain (> 3 months)
- First symptoms < 45 years of age

**Inflammatory back pain**
- sensitivity: 75% specificity 76%
- about 1 out of 5 patients has axial SpA, if positive
- simple to apply: yes
- costs: low

**Sacroiliitis on any imaging**
- only if available
- not recommended for screening

**HLA-B27+**
- sensitivity: 80-90%, specificity 90%
- about 1 out of 3 patients has axial SpA, if positive
- simple to apply: yes
- costs: moderate (only once)

Refer to Rheumatologist

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

- Inflammatory back pain;
- HLA-B27 positivity;
- Sacroiliitis on imaging if available (X-rays or magnetic resonance imaging);
- Peripheral manifestations (arthritis, enthesitis, dactylitis);
- Extra-articular manifestations (psoriasis, inflammatory bowel disease, uveitis);
- Positive family history for SpA;
- Good response to non-steroidal anti-inflammatory drugs;
- Elevated acute phase reactants.
AS vs. nr-axSpA
Similarities and Differences between Ankylosing Spondylitis (AS) and Non-radiographic Axial SpA (nr-axSpA)

<table>
<thead>
<tr>
<th></th>
<th>GESPIC&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Herne-Cohort&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All AS</td>
<td>AS ≤5 years</td>
</tr>
<tr>
<td></td>
<td>N=236</td>
<td>N=119</td>
</tr>
<tr>
<td>Age, years</td>
<td>35.6</td>
<td>36.1</td>
</tr>
<tr>
<td>HLA-B27 (+), %</td>
<td>82.2</td>
<td>73.1</td>
</tr>
<tr>
<td>Female, %</td>
<td>36.0</td>
<td>34.5</td>
</tr>
<tr>
<td>BASDAI (0-10)</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Total pain (0-10)</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td>BASFI (0-10)</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Patient’s global (0-10)</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Abnormal CRP, %</td>
<td>51.9</td>
<td>49.6</td>
</tr>
</tbody>
</table>

<sup>§</sup>p < 0.05 vs AS ≤5 years, <sup>*</sup>p < 0.05 vs AS


ASAS
AS vs nr-axSpA

- 100 consecutive German axSpA patients treated with TNFi
- AS more likely to be male (77% vs. 32%)
- Duration of symptoms and time since diagnosis similar

<table>
<thead>
<tr>
<th>Table 2. Clinical characteristics of patients with nr-axSpA and AS*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Axial SpA</strong> (total group, n = 100)</td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Global pain (≥4)</td>
</tr>
<tr>
<td>Back pain (≥4)</td>
</tr>
<tr>
<td>BASDAI (≥4)</td>
</tr>
<tr>
<td>Patient’s global assessment (≥4)</td>
</tr>
<tr>
<td>Physician’s global assessment (≥4)</td>
</tr>
<tr>
<td>BASFI (≥3)</td>
</tr>
<tr>
<td>SF-36 MCS (≥40)</td>
</tr>
<tr>
<td>SF-36 PCS (≥40)</td>
</tr>
<tr>
<td>ASQoL (≥5)</td>
</tr>
</tbody>
</table>

- This is **non-radiographic** axSpA, **not** pre-radiographic axSpA
Comparison of AS and nr-axSpA

Compared to AS, nr-axSpA patients:
- More likely female
- Similar burden of disease
- Similar biologic requirement
- Lower acute phase reactants
- More FM

nr-axSpA pts have clinical features that differentiate them from AS pts
Do AS pts differ from nr-axSpA? Corrona PsA/SpA registry

Clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AS (n=310)</th>
<th>nr-axSpA (n=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>34%</td>
<td>43%</td>
</tr>
<tr>
<td>Age, y, mean</td>
<td>49</td>
<td>44†</td>
</tr>
<tr>
<td>Disease duration, y, mean</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>HLA-B27+</td>
<td>66%</td>
<td>82%*</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>29%</td>
<td>47%‡</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td>Work impairment (WPAI)</td>
<td>26%</td>
<td>31%</td>
</tr>
</tbody>
</table>

nr-axSpA younger, more women, but clinical characteristics, QoL, disability, and work impairment similar to AS

Patient-reported outcomes

![Graph showing mean scores for various patient-reported outcomes between AS and nr-axSpA]
Comparing AS and nr-AxSpA: DANBIO

- 1250 axSpA pts from DANBIO registry
  - 50% AS, 29% nr-axSpA, 21% no SI radiographs
- Similar baseline activity
- Similar responses to TNFi
- HLA-B27+ pts had longer adherence, better response

Response to TNFi in AS vs nr-axSpA

- 86 nr-axSpA pts, 238 AS pts from southern Sweden
- Similar baseline parameters, similar response to therapy
- More women, lower CRP in nr-axSpA group
Gender and radiographic change

- Cross-sectional study of 235 consecutive patients meeting AS criteria from a Turkish clinic, not on TNFi
- Rapid progression - extensive radiographic change

Table 2. Demographic and clinical features of AS patients according to radiographic progression.

<table>
<thead>
<tr>
<th>Features</th>
<th>Slow Progression</th>
<th>Rapid Progression</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. women/men</td>
<td>85/88</td>
<td>15/47</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean age, yrs, ± SD</td>
<td>37.5 ± 11.0</td>
<td>44.0 ± 9.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Mean age at onset, yrs, ± SD</td>
<td>27.2 ± 9.7</td>
<td>27.5 ± 9.9</td>
<td>0.36</td>
</tr>
<tr>
<td>Mean disease duration, yrs, ± SD</td>
<td>10.6 ± 8.5</td>
<td>12.8 ± 8.7</td>
<td>0.09</td>
</tr>
<tr>
<td>Delay in diagnosis, yrs, ± SD</td>
<td>6.4 ± 7.1</td>
<td>7.8 ± 7.1</td>
<td>0.08</td>
</tr>
<tr>
<td>HLA-B27, %</td>
<td>63</td>
<td>86</td>
<td>0.005</td>
</tr>
<tr>
<td>Peripheral arthritis, %</td>
<td>47</td>
<td>21</td>
<td>0.001</td>
</tr>
<tr>
<td>Enthesitis, %</td>
<td>54</td>
<td>24</td>
<td>0.001</td>
</tr>
<tr>
<td>Hip involvement, %</td>
<td>53</td>
<td>46</td>
<td>0.35</td>
</tr>
<tr>
<td>Uveitis, %</td>
<td>20</td>
<td>28</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Gender and radiographic change

- Cross-sectional study of 619 patients meeting AS criteria
- Belgian cohort, mean disease duration 17.5 years

- Functional status not different for men, women – mobility?
- Similar findings in US PSOAS cohort

Patients with FM have worse AxSpA outcomes

- 1504 pts from BSRBR-AS
  - 311 met 2011 FM criteria
- FM patients worse on most outcome measures, more work impairment
- No difference in elevated CRP or extraspinal disease

### Table 2. Disease measures in patients with axial spondyloarthritis according to their meeting or not meeting the 2011 research criteria for FM*

<table>
<thead>
<tr>
<th>Disease index</th>
<th>Meeting 2011 criteria for FM</th>
<th>Not meeting 2011 criteria for FM</th>
<th>Difference (95% CI in mean score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASDAI activity</td>
<td>6.7 (6.5, 6.9)</td>
<td>3.6 (3.5, 3.8)</td>
<td>3.1 (2.8, 3.3)</td>
</tr>
<tr>
<td>BASFI function</td>
<td>6.6 (6.4, 6.9)</td>
<td>3.7 (3.6, 3.9)</td>
<td>2.9 (2.6, 3.3)</td>
</tr>
<tr>
<td>BASMI metrology</td>
<td>4.2 (4.0, 4.5)</td>
<td>3.6 (3.5, 3.8)</td>
<td>0.6 (0.3, 0.9)</td>
</tr>
<tr>
<td>BASG global health</td>
<td>6.9 (6.7, 7.2)</td>
<td>3.7 (3.6, 3.8)</td>
<td>3.2 (2.9, 3.6)</td>
</tr>
</tbody>
</table>

### Table 3. Patient-reported measures in patients with axial spondyloarthritis according to the 2011 research criteria for FM*

<table>
<thead>
<tr>
<th>Patient-reported measure</th>
<th>Meeting 2011 criteria for FM</th>
<th>Not meeting 2011 criteria for FM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASQoL quality of life</td>
<td>13.1 (12.7, 13.6)</td>
<td>6.1 (5.8, 6.4)</td>
</tr>
<tr>
<td>EQ-5D quality of life</td>
<td>0.45 (0.42, 0.48)</td>
<td>0.76 (0.74, 0.77)</td>
</tr>
<tr>
<td>HADS depression score</td>
<td>9.4 (8.9, 9.8)</td>
<td>4.6 (4.4, 4.8)</td>
</tr>
<tr>
<td>HADS anxiety score</td>
<td>11.0 (10.5, 11.5)</td>
<td>6.4 (6.2, 6.6)</td>
</tr>
<tr>
<td>SDS sleep</td>
<td>13.4 (12.7, 14.0)</td>
<td>8.1 (7.8, 8.4)</td>
</tr>
<tr>
<td>CFS fatigue</td>
<td>6.8 (6.4, 7.2)</td>
<td>2.8 (2.6, 3.0)</td>
</tr>
</tbody>
</table>

However, FM patients don’t meet AxSpA criteria

- 300 patients – 100 FM, 100 nrAxSpA, 100 AS
  - B27 available for 40 FM pts
- FM rarely met AxSpA criteria, up to 29% AxSpA met FM criteria

**Table 2** Classification according to different criteria sets

<table>
<thead>
<tr>
<th>Patient’s groups</th>
<th>Classification/diagnosis</th>
<th>ASAS classification criteria</th>
<th>2010 ACR FM criteria</th>
<th>1990 ACR FM criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>FM (n = 100)</td>
<td>2*/5†</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>axSpA (n = 200)</td>
<td>100</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>All axSpA patients</td>
<td>AS (n = 100)</td>
<td>100</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>nr-axSpA (n = 100)</td>
<td>100</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>All nr-axSpA patients</td>
<td>nr-axSpA—imaging arm (n = 69)</td>
<td>100</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>nr-axSpA—clinical arm (n = 31)</td>
<td>100</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Baraliakos et al. *Rheumatology* 2017; in press
Patients with FM respond less well to TNFi

- 526 pts initiating or switching TNFi
  - 202 (38%) screened as FM
  - 86 (16%) classified as FM
- BASDAI50 response lower in FM group
- No difference in CRP endpoints
Progression from nr-AxSpA to AS

- 83 Olmsted County pts with new-onset nr-axSpA
- During mean follow up 10.6 yrs, only 18 (26%) progressed to AS
- 28% of imaging arm progressed, vs 17% of clinical arm (p 0.02)
DESIR: SI progression in recent onset AxSpA

- 416 patients from DESIR cohort with baseline and 5-year sacroiliac (SI) radiographs\(^1\)
  - 14.9% baseline mNY AS
- 5.1% progressed from nr-axSpA to mNY AS
- Baseline SI inflammation on MRI predicted progression in both B27+ and B27-

AxSpA: Objective inflammation drives response

- 84 pts with objective inflammation, 84 matched pts without, followed over 15 yrs
  - All met ASAS clinical arm (B27+)
  - Objective inflammation included arthritis, enthesitis, uveitis, IBD, sacroiliitis, etc.
  - In multivariate analysis, MRI sacroiliitis was positive predictive factor of response, obesity negative
Inflammation may develop later

- Sub-analysis of 94 placebo-treated pts in ABILITY-1
  - 31% normal MRI at baseline
  - 61% normal CRP
  - 21% normal MRI and CRP
- 50% of the latter group had evidence of inflammation at 12 weeks

Fig. 1 Development of objective inflammation in placebo treated patients without baseline inflammation during 12 weeks

Baraliakos et al. Rheumatology 2017 In press
The term ‘non-radiographic axial spondyloarthritis’ is much more important to classify than to diagnose patients with axial spondyloarthritis

Atul Deodhar,¹ Vibeke Strand,² Jonathan Kay,³ Juergen Braun⁴
How does new classification affect therapy?
RAPID-AxSpA: CZP in AS/AxSpA

- First randomized, controlled trial of certolizumab pegol (CZP) in axSpA
- PBO controlled to week 24, dose-blind to week 48; then open-label to week 158
- Randomized 1:1:1 to PBO, 200 mg CZP q2W, or 400 mg CZP q4W after load

Clinical outcomes at week 12 for axSpA patients in RAPID-axSpA

<table>
<thead>
<tr>
<th></th>
<th>AxSpA</th>
<th>AS</th>
<th>nr-axSpA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASAS20</td>
<td>ASAS partial remission</td>
<td>ASAS20</td>
</tr>
<tr>
<td>PBO</td>
<td>38.3</td>
<td>3.7</td>
<td>40.0</td>
</tr>
<tr>
<td>CZP 200 mg q2W</td>
<td>57.7</td>
<td>23.4</td>
<td>56.9</td>
</tr>
<tr>
<td>CZP 400 mg q4W</td>
<td>63.6</td>
<td>24.3</td>
<td>64.3</td>
</tr>
</tbody>
</table>

CZP effective in AxSpA. Improvements similar in AS and nr-axSpA

ESTHER Trial: Etanercept in early AxSpA

- AxSpA <5 years of disease, with inflammatory changes on MRI

Comparing response with etanercept

- Phase III (AS) and EMBARK (nr-axSpA), 14 weeks
- Etanercept 50 mg qweek

<table>
<thead>
<tr>
<th></th>
<th>ASAS20</th>
<th>ASAS50/40</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etanercept</strong></td>
<td>59%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>28%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>AS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>nr-axSpA</strong></td>
<td>52%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>37%</td>
<td>15%</td>
</tr>
</tbody>
</table>

- Greater response in EMBARK in MRI+/CRP+ patients

Comparing response with golimumab

- GO-RAISE (AS) and GO-AHEAD (nr-axSpA), 14 weeks
- Golimumab 50 mg q4 weeks

<table>
<thead>
<tr>
<th></th>
<th>ASAS20</th>
<th></th>
<th>ASAS40</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Golimumab</td>
<td>Placebo</td>
<td>Golimumab</td>
</tr>
<tr>
<td>AS</td>
<td>59%</td>
<td>22%</td>
<td>44%</td>
</tr>
<tr>
<td>nr-axSpA</td>
<td>71%</td>
<td>40%</td>
<td>57%</td>
</tr>
</tbody>
</table>

- Greater response in GO-AHEAD in MRI+/CRP+ patients

Comparing response with adalimumab

- ATLAS (AS) and ABILITY-1 (nr-axSpA), 12 weeks
- Adalimumab 40 mg q2 weeks

<table>
<thead>
<tr>
<th></th>
<th>ASAS20</th>
<th>ASAS40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>58%</td>
<td>39%</td>
</tr>
<tr>
<td>Placebo</td>
<td>21%</td>
<td>13%</td>
</tr>
<tr>
<td>AS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nr-axSpA</td>
<td>52%</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>31%</td>
<td>15%</td>
</tr>
</tbody>
</table>

- Greater response in ABILITY-1 in MRI+/CRP+ patients

What about newer therapies?
SEC in AS with IV load: MEASURE 1

- 371 patients with active AS randomized to iv SEC at BL, Wk 2 and 4, and then SC SEC every 4 weeks

  - Response sustained in open-label extension through 52 weeks
  - Safety comparable to PSA trials

SEC effective in active AS; improvements sustained through 52 wks

*P<0.01 vs PBO; LSM, least square mean
Baeten D, et al. ACR 2014, Boston, #819
SEC SC in AS: MEASURE 2

- SEC 75 mg/SEC 150 mg/PBO weekly for 4 weeks, then monthly for 3 months
- 62% TNFi-naïve
- DD 6 y, mean BASDAI 6.7
- SEC 150 mg: improved ASAS4/5, BASDAI, SF-36, ASQoL and CRP in both TNFi-naïve and TNFi-IR
- SAEs: SEC 150 mg, 5.6%; PBO 4.1%

*P<0.0001; †P<0.001; § P<0.01; ‡P<0.05 vs PBO


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ACR responses in MEASURE 1 and 2: TNFi-naïve vs TNFi-IR patients

**MEASURE 1: TNFi-naïve**

<table>
<thead>
<tr>
<th>Group</th>
<th>ASAS20 Responders (%)</th>
<th>ASAS40 Responders (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEC 150</td>
<td>66</td>
<td>49</td>
</tr>
<tr>
<td>SEC 75</td>
<td>60</td>
<td>34</td>
</tr>
<tr>
<td>PBO</td>
<td>33</td>
<td>16</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>99</strong></td>
<td><strong>99</strong></td>
</tr>
</tbody>
</table>

**MEASURE 1: TNFi-IR**

<table>
<thead>
<tr>
<th>Group</th>
<th>ASAS20 Responders (%)</th>
<th>ASAS40 Responders (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEC 150</td>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td>SEC 75</td>
<td>59</td>
<td>21</td>
</tr>
<tr>
<td>PBO</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>88</strong></td>
<td><strong>88</strong></td>
</tr>
</tbody>
</table>

**MEASURE 2: TNFi-naïve**

<table>
<thead>
<tr>
<th>Group</th>
<th>ASAS20 Responders (%)</th>
<th>ASAS40 Responders (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEC 150</td>
<td>68</td>
<td>18</td>
</tr>
<tr>
<td>SEC 75</td>
<td>51</td>
<td>43</td>
</tr>
<tr>
<td>PBO</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>134</strong></td>
<td><strong>134</strong></td>
</tr>
</tbody>
</table>

**MEASURE 2: TNFi-IR**

<table>
<thead>
<tr>
<th>Group</th>
<th>ASAS20 Responders (%)</th>
<th>ASAS40 Responders (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEC 150</td>
<td>50</td>
<td>26</td>
</tr>
<tr>
<td>SEC 75</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>PBO</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>84</strong></td>
<td><strong>84</strong></td>
</tr>
</tbody>
</table>

Slightly lower efficacy of SEC in TNFi-IR population


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# Tofacitinib in AS

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Primary efficacy endpoint results: ASAS20 response rate at week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=51</td>
</tr>
<tr>
<td>Emax model-predicted ASAS20 response, %†</td>
<td>40.1</td>
</tr>
<tr>
<td>Estimated treatment difference from placebo</td>
<td>–</td>
</tr>
<tr>
<td>95% credible interval</td>
<td>–</td>
</tr>
<tr>
<td>60% credible interval</td>
<td>–</td>
</tr>
<tr>
<td>50% credible interval</td>
<td>–</td>
</tr>
</tbody>
</table>
2016 ASAS-EULAR treatment recommendations for axSpA

- Updated to address new therapies
- 5 overarching principles and 13 recommendations
- NSAIDs remain first-line therapy
- Key updates:
  - Included IL-17 inhibitors (start with TNFi)
  - Biologics indicated for pts with high disease activity and MRI inflammation and/or elevated CRP
  - Continue at least 12 weeks before considering a switch
  - Taper, but do not stop, if sustained remission

Rheumatologist’s diagnosis of axSpA
and
Elevated CRP and/or positive MRI and/or radiographic sacroiliitis*
and
Failure of standard treatment:
- **All patients**
  - At least 2 NSAIDs over 4 weeks (in total)
- **Patients with predominant peripheral manifestations**
  - 1 local steroid injection if appropriate
  - Normally a therapeutic trial of sulfasalazine
and
High disease activity: ASDAS ≥2.1 or BASDAI ≥4
and
Positive rheumatologist’s opinion

*Radiographic sacroiliitis is mandatory for infliximab and IL-17i
View of nr-axSpA by regulatory agencies

- US: TNF inhibitors approved for AS, *not* axSpA (i.e., not nr-axSpA)
- Australia: etanercept, golimumab approved for treatment of axSpA
- NZ: etanercept, adalimumab approved for treatment of axSpA
- Europe: all approved for treatment of axSpA *with evidence of inflammation* (*MRI or elevated CRP*)
What about progression?
TNFi use and spinal radiographic progression

• Prospective study of 334 AS pts, 201 treated with TNFi
  – All had at least 2 spinal radiographs at least 2 years apart
• Use of TNFi (uncontrolled) associated with lower rate of mSASSS progression
• TNFi treated patients had higher baseline BASDAI, more likely male
TNFi use and spinal radiographic progression

- Observational Dutch cohort of 210 AS patients treated with TNFi
- Planned radiographs every 2 years
  - 45 had 2 year radiographs
- Apparent deflection in rate of progression after 4 years of therapy

<table>
<thead>
<tr>
<th>Table 3. Baseline damage and spinal radiographic progression in ankylosing spondylitis patients with complete data over 4, 6, or 8 years of followup (observed data)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mSASSS data</strong></td>
</tr>
<tr>
<td>Complete 4-year</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Complete 6-year</td>
</tr>
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<tr>
<td></td>
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<tr>
<td>Complete 8-year</td>
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</tr>
</tbody>
</table>

* IQR = interquartile range; mSASSS = modified Stoke Ankylosing Spondylitis Spine Score.
325 pts from RAPID-AxSpA trial of AS and nr-AxSpA

Rapid resolution of MRI inflammation in both groups

Limited radiographic progression in either group

4.5% of nr-AxSpA pts fulfilled mNY criteria for AS at 4 years, while 4.3% of AS pts no longer did.

van der Heijde D et al. *ARD* 2018; Epub ahead of print
Low functional relevance of progression in early axSpA

- GESPIC cohort: patients not on Rx apart from NSAID
- BASDAI, BASMI, BASFI at baseline and every 6 months
- Structural: spinal radiographs mSASSS (max score 72)
- Linear regression analysis mixed model
- 2-year progression of 25 mSASSS points equated to a 1-point difference in BASFI

![Association between mSASSS Δ and BASFI Δ over 2 years in patients with early axSpA](image)

Structural progression on radiographs does not correspond to changes in function over 2 years

Poddubnyy D et al. ACR 2016, Washington DC, #677
Conclusions

• Non-Radiographic Axial Spondyloarthritis is really a regulatory construct, rather than a separate disease
• With some exceptions (CRP, gender), nr-axSpA is clinically similar to AS
• Clinical response to TNF inhibitors is similar for AS and nr-axSpA, particularly for nr-axSpA patients with MRI inflammation and/or elevated CRP
• Regulatory agencies differ in their approach. In the U.S., the FDA has approved biologic therapies only for AS
• We still haven’t identified therapies with a convincing, meaningful impact on progression
Questions?