Update in Axial Spondyloarthritis and Ankylosing Spondylitis

Sergio Schwartzman, MD
Franchellie M. Cadwell
Associate Professor of Medicine
Weill Medical College of Cornell University
The Hospital for Special Surgery
New York Presbyterian Hospital
New York, NY
The Hospital for Special Surgery
Disclosures

• Consultant:
  – Abbvie, Antares, Genentech, Janssen, Lilly, Novartis, Pfizer, Regeneron, Sanofi, UCB

• Speaker:
  – Abbvie, Janssen, Genentech, Pfizer, UCB, Crescendo, Novartis

• Board Member:
  – Crescendo Biosciences
  – National Psoriasis Foundation
Objectives

• Understand the evolving definition, immunology, genetics and classification of ankylosing spondylitis (AS) and axial spondyloarthritis (SpA)

• Comprehend established and new therapies for AS and axial spondyloarthritis
Agenda

• Background – Group of Overlapping Diseases
• Classification
• Genetics (HLA-B 27) and Potential Causes
• Treatment
Spondyloarthritis: A Family of Related Diseases

- Undifferentiated Spondyloarthritis
- Reactive Arthritis (Reiter's Syndrome)
- Juvenile Spondyloarthritis
- Arthritis Associated with Inflammatory Bowel Disease (Enteropathic Arthritis)
- Psoriatic Arthritis
- Ankylosing Spondylitis

Overlapping Illnesses - Now Termed Spondyloarthritis

Spondylitis Association of America.
Entheses – Attachment of a Tendon or a Ligament to Bone

Spondyloarthritis

Axial SpA
- AS
- nr-AxSpA

Peripheral SpA
- PsA
- IBD-related SpA
- Reactive arthritis
- Undifferentiated SpA

Common clinical features
- Asymmetric peripheral arthritis
- Enthesitis
- Inflammatory back pain
- Extra-articular involvement
Natural History Ankylosing Spondylitis

Causation

• In the correct genetic host and with the correct precipitants → Malfunctioning of the **Innate and Adaptive** immune response

• Three overlapping elements:
  • Enthesitis
  • Bone erosion
  • Inappropriate bone formation → Syndesmophyte formation and fusion

• IL23, IL-17 and TNF
  – Enthesitis occurs via the IL-23/IL-17 axis
  – TNFα direct effects on bone erosion
  – IL-17 direct effects on bone formation and bone erosion
Genetics - HLA B-27

- In the United States, approximately 6% of the population is HLAB-27 positive

- Approximately 5% of patients with HLAB-27 develop AS

- Heritability for >90% in AS – twin studies

Epidemiology

- Prevalence: Varies by country and background

- Gender ratios of around 2:1 (male:female)

How Does HLA B27 Cause Spondyloarthritis

- **Molecular Mimicry** virus or bacteria copies the body
- **Inability to Clear Infectious Agents**
- **Misfolding in the ER** – inflammatory peptide
- **Microbiome**
Comparison of AS, SpA and RA

The Spectrum of Axial SpA
Pre-Radiographic Stage (MRI abnl, undifferentiated SpA)*

Radiographic Stage
Modified New York Criteria (1984)*

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Radiographic Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back Pain</td>
<td>Back Pain</td>
</tr>
<tr>
<td></td>
<td>Radiographic Sacroiliitis</td>
</tr>
<tr>
<td></td>
<td>Syndesmophytes</td>
</tr>
</tbody>
</table>

Patients with chronic back pain ≤3 months and age of onset <45 years

<table>
<thead>
<tr>
<th>Non-Radiographic Stage</th>
<th>Radiographic Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray-negative</td>
<td>X-ray-positive sacroilitis</td>
</tr>
</tbody>
</table>

*Clinical arm if non-radiographic axial SpA; **Radiographic evidence of inflammatory spinal changes, including for example, syndesmophytes, fusion, or posterior element involvement.

The Spectrum and Natural History of SpA

- Subclinical process in genetically predisposed patients
- Inflammatory back pain
- Spontaneous remission
- nr-AxSpA
- Quiescent disease activity
- AS
- Nonprogressing AS
- AS late complications

Symptoms

- Onset of back pain before the age of 45 that persists over 3 months, that is at its worst in the mornings and during the night. It improves with exercise
- Tendinitis and fasciitis
- Fatigue, fever, loss of energy
- Eye inflammation - Uveitis
Delay in Diagnosis - Age at Onset of Symptoms and Age at Diagnosis in AS

From first symptoms to diagnosis: 5-10 yrs

Outcome Measures

**BASDAI**

1. How would you describe the overall level of fatigue/tiredness you have experienced?
   - NONE .................................................. VERY SEVERE

2. How would you describe the overall level of AS neck, back or hip pain you have had?
   - NONE .................................................. VERY SEVERE

3. How would you describe the overall level of pain/swelling in joints other than neck, back, hips you have had?
   - NONE .................................................. VERY SEVERE

4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?
   - NONE .................................................. VERY SEVERE

5. How would you describe the overall level of morning stiffness you have had from the time you wake up?
   - NONE .................................................. VERY SEVERE

6. How long does your morning stiffness last from the time you wake up?
   - __________________________________________
     0 hrs  ½  1  1½  2 or more hours

AS Spectrum Comanifestations and Comorbidities

Eye
- Acute Anterior Uveitis

Gut
- Enteric Mucosal Lesions
  - Ileal and colonic mucosal ulcerations
  - May affect 40%-50% of patients
- Psoriasis

Skin
- Psoriasis

Heart
- Aortic regurgitation, ascending aortitis, aortic valve incompetence, conduction abnormalities, cardiomegaly, and pericarditis

Lung
- Apical pulmonary fibrosis

Osteoporosis

Cardiovascular Ds

Fibromyalgia

References:
Uveitis in Spondyloarthritis

- 30% to 40% of patients with AS over their lifetime develop anterior uveitis
- Often unilateral presentation but can be bilateral
- Anterior, Acute and Recurrent

http://www.geteyesmart.org/eyesmart/diseases/uveitis/.
Association Between Inflammatory Bowel Disease and SpA

- Familial Clustering
- Genetic - HLA-B27, NOD2/CARD15, IL-23R
- Cytokines - TNF–α, IL-12, IL-23, and IL-17?
- Microbiome Associations
- Similar precipitants – infection, trauma, “stress”
- Overlapping Treatments
SpA prevalence rates between 17 to 39% have been reported in IBD
SpA Prevalence in IBD

- SpA prevalence rates between 17 to 39% have been reported in IBD

- In patients with different forms of SpA approximately 60% have gut inflammation “microscopic colitis”

- 5 - 12% of SpA patients will develop overt IBD

- Routine screening is not recommended as only a small percentage develop overt IBD

Treatment: AS and Bowel Disease

- Differential effects of anti-TNF therapies

- Infliximab, certolizumab, golimumab and adalimumab are used in treating clinical symptoms, inducing and maintaining remission, and mucosal healing

- Can NSAIDs exacerbate IBD?

Comorbidities

- **Osteoporosis** - Prevalence between **19 and 50%** - Inflammation and immobilization

- **Cardiovascular** - Age-adjusted and sex-adjusted **HR of 1.60** accounting for **34.7% of all deaths**

- **Fibromyalgia** - BSRBR-AS, (AS and AxSpA) **1,504 (68% male)** - **20.7% met the 2011 research criteria for FM**
Treatment Recommendations

American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis

Recommendations

- Strongly Recommend **NSAID continuously**, conditionally recommend on-demand
- Strongly recommend **TNFi – allowances for IBD and Uveitis**
- Strongly recommend against **systemic steroids**
- Conditionally recommend against **SAARDs**
- Strongly recommend **Physical Therapy**
- Strongly recommend **THR**
- Conditionally recommended treating **nr-AxSpA with TNFi**
- **Tendon injections** should be avoided
Efficacy of Sulfasalazine (Cochrane Meta-Analysis)

11 Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Some Evidence of Benefit</th>
<th>No Evidence of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ESR</td>
<td>• Physical function</td>
</tr>
<tr>
<td>• Morning stiffness</td>
<td>• Pain</td>
</tr>
<tr>
<td>• Peripheral arthritis (2 trials)</td>
<td>• Spinal mobility</td>
</tr>
<tr>
<td></td>
<td>• Enthesitis</td>
</tr>
<tr>
<td></td>
<td>• Patient and physician global assessment</td>
</tr>
</tbody>
</table>

**Conclusion:**
Patients with early disease, with higher levels of ESR, and peripheral arthritis may benefit

## Efficacy of Methotrexate (Cochrane Meta-Analysis)

### Conclusions:
- MTX demonstrated no statistically significant benefit.
- Additional randomized controlled trials with larger samples, longer duration, and higher MTX dosages are needed.

### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>MTX + Naproxen vs Naproxen</th>
<th>MTX vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral arthritis/enthesitis</td>
<td>No significant difference</td>
<td></td>
</tr>
<tr>
<td>Morning stiffness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP and ESR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2 Randomized Controlled Trials (N=81)

Do NSAIDs really reduce radiographic progression AS patients...and how should these be administered?


Do NSAIDs really reduce radiographic progression AS patients…and how should these be administered?

NSAIDs on-demand treatment group (n=104) vs. continuous treatment group (n=111) over 2 years\(^1\)
Radiographic progression was \(0.4\pm1.7\) in the continuous treatment group vs. \(1.5\pm2.5\) in the on-demand treatment group \((p=0.002)\)\(^1\)

NSAIDs (diclofenac) on-demand treatment group (n=60) vs. continuous treatment group (n=62) over 2 years\(^2\)
Radiographic progression was \(1.28\) in the continuous treatment group vs. \(0.79\) in the on-demand treatment group. The difference was numerical higher in the continuous group, but not statistically significant\(^2\).


*Modified Stoke AS Spine Score. NS: Not significant; GI: Gastrointestinal
Clinical improvements in AS after 24 weeks of TNF inhibitor treatment

Response after 24 weeks of TNF inhibitor treatment in AS

*Different studies, not head to head comparisons

IL-17 Secukinumab in AS

**MEASURE 2**

- Responses were similar in patients regardless of concomitant therapies

<table>
<thead>
<tr>
<th>ASAS20 and ASAS40 at week 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secukinumab</td>
</tr>
<tr>
<td>COSENTYX 150 mg (n=72)</td>
</tr>
<tr>
<td>61%</td>
</tr>
<tr>
<td>36%</td>
</tr>
<tr>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

- All patients received an initial once-weekly x5 weeks loading dose

**MEASURE 1: 4 years**

*mSASSS: cumulative probability of progression*

- Secukinumab 10 mg/kg IV → 150 mg SC (n=71)
- Secukinumab 10 mg/kg IV → 75 mg SC (n=84)
IL-17 Ixekizumab - COAST V - Results

ASAS responses over 16 weeks. \( p < .01; \) \( p < .001 \). A logistic regression model was used for comparisons between placebo and active treatment arms. Missing data were considered as nonresponse. Adalimumab represents an active reference; the study was not powered to
IL-17 COAST W – Objective Outcomes

**MRI SPARCC Spine Score**

- **PBO (N=81)**
- **IXE Q4W (N=63)**
- **IXE Q2W (N=59)**

<table>
<thead>
<tr>
<th>LSM Change From Baseline</th>
<th>3.3</th>
<th>-3.0</th>
<th>-4.0</th>
</tr>
</thead>
</table>

**High Sensitivity CRP**

- **PBO (N=104)**
- **IXE Q4W (N=114)**
- **IXE Q2W (N=98)**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSM Change From Baseline</td>
<td>9.7</td>
<td>-8.1</td>
<td>-11.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<.01, †p<.001 vs PBO*
Newer Therapies

- Tofacitinib
- Baricitinib
- IL-17 Ixekizumab
- Tildrakrisumab
Tofacitinib for Biologic-Naïve Patients with AS

- Randomized, double-blind, placebo-controlled, dose-ranging phase 2 trial
- Tofacitinib: oral JAK inhibitor

Baseline characteristics
- Mean disease duration: 1.5-4.1 years; mean BASDAI total score, 6.3-7.0
- Concomitant DMARDs: 27.5%-44.2%

Tofacitinib for AS: Results

<table>
<thead>
<tr>
<th>Week 12, %</th>
<th>Tofacitinib</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 mg (n=52)</td>
<td>5 mg (n=52)</td>
</tr>
<tr>
<td>ASAS20 response (Eₘₐₓ model)*</td>
<td>56.0</td>
<td>63.0</td>
</tr>
<tr>
<td>Difference vs PBO (95% CI)</td>
<td>15.8 (5.0-30.3)</td>
<td>22.9 (8.4-37.7)</td>
</tr>
<tr>
<td>ASAS20 (observed)</td>
<td>51.9</td>
<td>80.8†</td>
</tr>
<tr>
<td>BASDAI 50</td>
<td>46.2‡</td>
<td>42.3‡</td>
</tr>
<tr>
<td>DC for AE</td>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>TEAEs</td>
<td>44.2</td>
<td>53.8</td>
</tr>
<tr>
<td>SAEs</td>
<td>0</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*Primary endpoint. †P<.001 vs PBO. ‡P<.05 vs PBO.

- Tofacitinib treatment also associated with improvements in ASDAS, SPARCC MRI (joint and spine)
• **Apremilast** - Posture Study - ASAS20 Response at Week 16: Placebo (164) 36.6% Apremilast (163) 32.5%¹

• **Abatacept** – Pilot study, in TNF naïve and TNFi IR. Week 24, ASAS40 was reached by 13% of group TNF naive and 0% of group TNF Exp; ASAS20 was reached by 27% and 20%, respectively³

• **Ustekinumab** - Study 1 [anti-tumor necrosis factor (TNF)-naïve]; Study 2 [anti-TNF refractory], and Study 3 non-radiographic axSpA²

• **Risankizumab** - Wk 12, ASAS40 response rates were 25.5%, 20.5% and 15.0% in the 18 mg, 90 mg and 180 mg compared with 17.5% Placebo

• **Guselkumab** – No studies being done

• **Tocilizumab** – ASAS 20 Wk 12, 37.3% vs 27.5 % placebo ASAS40 11.8% vs 19.6% placebo⁴

---

C-axSpA - Certolizumab for nr-Axial SpA

317 Pts axSpA without radiographic evidence AS
400 mg dose of subcutaneous CIMZIA or placebo at baseline and at 2 and 4 weeks, followed by 200 mg of CIMZIA every 2 weeks thereafter

ASDAS-MI; defined as ASDAS decrease from BL ≥2.0 points or reaching lowest possible value
Brussels, Belgium – 28 March 2019 – UCB, a global biopharmaceutical company, announced today that the U.S. Food and Drug Administration (FDA) has approved extending the label for CIMZIA® (certolizumab pegol) to include a new indication for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation. The approval makes CIMZIA the first and only FDA-approved treatment for nr-axSpA.
Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab.

Cumulative percentages of Retreatment after discontinuation of infliximab in AS.

41/42 patients responded and reached a disease state similar to when treatment was discontinued.

Conclusions

• Axial Spondyloarthritides are joint and enthesial diseases that have a predilection for affecting the axial skeleton. There are distinctive clinical presentations and extra-articular manifestations.

• The new axial and peripheral SpA criteria have broadened our view of this group of diseases

• The genetics and immunology are being increasingly understood

• Therapies targeting SpA have dramatically affected the lives of patients and provided therapeutic choices

• Research into new therapy and biomarkers continues to evolve