Management of Spondyloarthritis

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WWW.HLAB27.COM
Consultant: Lilly, Abbvie, Novartis

Speakers Bureau: Abbvie, Novartis

Ownership Interest: None
Topics for Discussion

- Nomenclature
- Clinical manifestations
- Disease in women
- Early referral and diagnosis
- Management
Tse, S. M. L. & Laxer, R. M. New advances in juvenile SpA.
JUVENILE SPONDYLOARTHROPATHIES

IBD
ReA
PsA
SEA syndrome
JAS
ERA

JUVENILE SPONDYLOARTHROPATHIES

ADULTS

u-SpA

Inflammatory back pain
Sacroiliitis by X-ray

Peripheral arthritis
enthesitis

CHILDREN

AS

JAS

ONSET
Spondyloarthritis (SpA)

- Undifferentiated SpA
- Juvenile SpA
- Enteropathic SpA
- Reactive SpA
- Psoriatic SpA
- Sacroiliitis

Multi-factorial
Genetic
Environmental
(non-genetic and socio-economic factors)

AAU = acute anterior uveitis.
AI+HB = aortic incompetence plus heart block

Adapted from
Elyan M, Khan MA. *J Rheumatol* 2006; 33 Suppl 78: 12-23.
Patients With axSpA Can Be Divided Into Two Main Subgroups: nr-axSpA and r-axSpA (AS)

Some but not all patients with nr-axSpA progress to AS over time

NrAxSpA = non-radiographic axial SpA, PsA = psoriatic arthritis. AAU = acute anterior uveitis. AI+HB = aortic incompetence plus heart block. Miscellaneous entities not shown, include FMF (familial Mediterranean fever), and SAPHO and Behcet’s syndrome.
AxSpA in Women vs Men

Recent studies show almost equal prevalence of axSpA among males and females, especially among patients with nr-axSpA.

A very recent study from Switzerland found that over the last four decades, the estimated disease prevalence in males and females has gradually equalized.


Clinical and Pathological Features of SpA

Enthesitis, Arthritis, Tendonitis, Tenosynovitis, Periostitis, Dactylitis, Sacroiliitis, Spondylitis, Ankylosis

ENTHESITIS

SYNOVITIS

OSTEITIS

OSTEOPENIA

BONE RESORPTION

EROSION

REACTIVE

OSTEOSCLEROSIS

BONE REMODELING

OSTEOPROLIFERATION

ANKYLOSIS

AS / Axial SpA: Associated Manifestations/Comorbidities

Axial disease
Enthesitis
Peripheral arthritis
Dactylitis

Aberrant Ossification
Juxtaposed with Osteopenia/Osteoporosis
19 to 62%

Acute Anterior Uveitis
25 – 45%

Skin
Psoriasis & Nail Changes
5 – 16%

Gut
UC & Crohn 5 – 8%
(Microscopic lesion 22 – 69%)

Lung
Restrictive Lung Disease
Apical Fibrocystic Disease 1 – 2%
Obstructive sleep apnea

Heart
Aortic Insufficiency / Heart Block
2 – 3%
Increased risk CAD as a result of chronic inflammation and inactivity
Hypertension
NSAID induced risks

Kidneys
IgA nephropathy 1 to 2%
Renal amyloidosis 0.3 – 1.2%
NSAID induced nephropathy

Cauda Equina Syndrome 0.5%

Spinal Ankylosis
Spinal fracture
Atlantoaxial subluxation

Patient Education

Physical therapy and rehabilitation training

Lifelong exercise program

Lifestyle and employment modification

Complete avoidance of smoking

Dr. Google & the iSNAKE Oil
2010 ASAS/EULAR Recommendations for the Management of AS

- High to moderate quality evidence indicates that both traditional and COX-2 NSAIDs are efficacious.
- Moderate to low quality evidence indicates harms may not differ from placebo in the short term.
- Various NSAIDs are not equally effective for an individual patient.
- Etoricoxib > Naproxen

2015 Jul 17;7:CD010952. [Epub ahead of print]
2010 ASAS*/EULAR Recommendations for the Management of AS

Patient Education
- Exercise
- Physical therapy
- Rehabilitation,
- Patient associations & self-help groups

NSAIDs
- Axial disease
- Peripheral disease
- One DMARD, preferably SSZ
- Local C/S injection
- TNFi
- IL-17i

Analgesics
Surgery


*ASAS = Assessment in Spondyloarthritis International Society
Conventional DMARDs Are Largely Not Effective for the Treatment of Patients with AS

**Sulfasalazine**
- 2 g/day

**Leflunomide**
- 20 mg/day

**Methotrexate**
- 20 mg/week sc

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Pamidronate in AS

Randomized, "double-blind", controlled trial
IV pamidronate (60 mg/month), 6 doses
Reduced BASDAI by 35%, but no change in ESR, CRP


Clinical response rate and improvement in pain and QoL were similar after 48 weeks. But significant reduction in inflammatory markers and MRI inflammation was only observed with GLM treatment.


Thalidomide: in China

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Drug target</th>
<th>US status</th>
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</thead>
<tbody>
<tr>
<td>Novartis (Basel)</td>
<td>Secukinumab (Cosentyx)</td>
<td>IL-17A</td>
<td>• Approved for PsO (2015)</td>
</tr>
<tr>
<td></td>
<td>Human</td>
<td></td>
<td>• Approved for AS &amp; PsA (2016)</td>
</tr>
<tr>
<td>Janssen (New Jersey)</td>
<td>Ustekinumab (Stelara)</td>
<td>IL-12/23 p40</td>
<td>• Approved for PsO (2009)</td>
</tr>
<tr>
<td></td>
<td>Human</td>
<td></td>
<td>• Approved: Active PsA (2013)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Not effective in AS</td>
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</tbody>
</table>

Ratner M. *Nature Biotechnology*. 2014; 35:505-7
<table>
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<th>Company</th>
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</thead>
</table>
| Pfizer (New York) | **Tofacitinib** (Xeljanz) | JAK3        | • Approved for PsO and PsA  
• Phase 3 studies in AS. |
| Celgene (New Jersey) | **Apremilast** (Otezla) | PDE4        | • Approved for PsO and PsA  
• Phase 2 study in AS published |

- [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT01860976), Efficacy and Safety of Subcutaneous Ablatacept in Adults With Active Psoriatic Arthritis (ASTRAEA).
- [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT01786668), Dose-Ranging Study Of Tofacitinib In Adults With Active Ankylosing Spondylitis.
- [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT01877668), Efficacy And Safety Of Tofacitinib In Psoriatic Arthritis: Comparator Study (OPAL BROADEN).
- [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT01583374), Study of Apremilast to Treat Subjects With Active Ankylosing Spondylitis (POSTURE).
- [Alder.com](http://www.alderbio.com/therapeutics/pipeline/), Pipeline.
Biologics other than TNF-inhibitor in AS

**Rituximab** (anti-CD20 monoclonal antibody): Some response in TNF-inhibitor naïve patients with active AS, but not in those who failed TNF-inhibitors
(Possible mild efficacy in PsA in a open-label study of 9 patients)

**Abatacept** (**Orencia**): Not effective in AS

**Tocilizumab** & **Sarilumab** (**IL-6R antagonists**): Not effective in AS

**Anakinra** (anti-IL-1): Not effective in AS

References:

Patients demonstrating at least 2 mSASSS units progression after 2 years

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<thead>
<tr>
<th>Syndesmophytes present</th>
<th>Non-smoker</th>
<th>Smoker</th>
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<tbody>
<tr>
<td>40% (n=6)</td>
<td>55% (n=11)</td>
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<tr>
<td>19% (n=16)</td>
<td>33% (n=15)</td>
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<table>
<thead>
<tr>
<th>Syndesmophytes not present</th>
<th>Non-smoker</th>
<th>Smoker</th>
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<tbody>
<tr>
<td>7% (n=31)</td>
<td>20% (n=15)</td>
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<tr>
<td>4% (n=71)</td>
<td>13% (n=45)</td>
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**Smoking:**
An environmental risk factor for worse outcome

Disease activity in male smokers has a >10-fold amplified effect on radiographic damage in comparison with female non-smokers in AS.


Radiographic Progression

Strongly dependent on the following risk factors:

- Genetics (HLA-B27)
- Gender (more in males vs females)
- Environmental (smoking)
- Inflammatory (MRI positivity)
- Syndesmophytes at baseline
- Hip joint involvement
- Elevated CRP &/or ESR

Stolwijk C, et al. ACR 2013 Meeting Poster. (In smokers 5-fold worsening; 13.5 fold in males vs females)
The Link Between Gut & SpA

- Approximately 50 to 60% of AS patients exhibit signs of microscopic gut inflammation.
- Chronic gut inflammation predicts a higher risk of evolving to AS.
- Remission of joint disease is associated with reduced bowel inflammation and vice versa. Therapies targeting inflammation at both sites may, therefore, be beneficial in AS patients with gut inflammation.
- There are currently insufficient data from human studies to make clinical recommendations with respect to therapeutic modulation of the microbiota by diet, probiotics, prebiotics or antibiotics.
ASDAS (Ankylosing Spondylitis Disease Activity Score)

<table>
<thead>
<tr>
<th>Parameters used for calculation of the ASDAS</th>
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<tr>
<td>1. Total back pain (BASDAI question 2)</td>
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<td>2. Patient global</td>
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<tr>
<td>3. Peripheral pain/swelling (BASDAI question 3)</td>
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<tr>
<td>4. Duration of morning stiffness (BASDAI question 6)</td>
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<td>5. CRP in mg/l (or ESR)</td>
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Need for a Treat to Target (T2T) Approach

- **< 1.3**: Inactive disease
- **< 2.1**: Low disease activity
- **> 3.5**: Very high disease activity

A free app available from [www.asas-group.org](http://www.asas-group.org)

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# Newer Treatments Being Developed for SpA

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<th>Company</th>
<th>Drug</th>
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</table>
| Janssen/Covagen (NJ/Switzerland) | **COVA322**  | TNF/IL-17A      | • Phase 1/2 in PsO  
• Preclinical in PsA  
• Preclinical in AS |
|                          | Fully Humanized, Bispecific |                |                                                |

![Diagram of COVA322](image)

| AbbVie (Chicago) | **ABT-122**  | TNF/IL-17A      | • Phase 1 completed in RA  
• Phase 2 in PsA |
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<tbody>
<tr>
<td></td>
<td>Fully Humanized, Bispecific</td>
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</table>

- Clinicaltrials.gov: A Phase 2 Study to Investigate the Safety, Tolerability and Efficacy of ABT-122 in Subjects With Active PsA Who Have an Inadequate Response to MTX; [https://clinicaltrials.gov/ct2/show/NCT02349451](https://clinicaltrials.gov/ct2/show/NCT02349451)
- Clinicaltrials.gov: Dose Ranging Study Comparing the Efficacy, Safety and Pharmacokinetics of Intravenous Infusions of ABT-874 vs Placebo in Subjects With Active Crohn’s Disease [https://clinicaltrials.gov/ct2/show/NCT00562887](https://clinicaltrials.gov/ct2/show/NCT00562887)
Concluding Remarks

• SpA much more common than previously thought; form a heterogeneous group; today’s talk focused on AS.

• Early diagnosis is now more important for maximizing QoL and retarding disease progression because much more effective treatments are now available.

• Closer cooperation between relevant health care providers is crucial for early referral to facilitate early diagnosis and appropriate treatment.