Axial spondyloarthritis and psoriatic arthritis: emerging treatment strategies

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Disclosure

• Competing interests: none
Spondyloarthropathies

• a family of seronegative diseases that share certain clinical features:
  – inflammation of axial joints
  – asymmetric oligoarthritis
  – enthesitis
  – eye and bowel inflammation

• a strong association with HLA-B27
Spondylarthritis:

- **SHARED FEATURES**
- **HIGHLY HETEROGENEOUS PHENOTYPES**

**SPONDYLARTHRITIS family**

- **Skin (psoriasis)**
- **Axial skeleton**
- **Peripheral arthritis**
- **Gut (IBD)**
- **Eye (uveitis)**
- **sero-negativity**
- **Genetic risk factors**
  - HLA-B27
  - IL-23R
  - ERAP1
  - strong familial aggregation

**SHARED FEATURES**

- **HIGHLY HETEROGENEOUS PHENOTYPES**

**Immunopathology**

- **enthesitis & dactyitis**

**Gene associated risk factors**
## Classifications of the SpA family

### Traditional
- Ankylosing spondylitis
- Psoriatic SpA
- Enteropathic SpA
- Reactive arthritis (infection-associated)
- Juvenile-onset SpA
- Undifferentiated

### Current

**Predominantly axial** (spine, pelvis & thoracic cage)
- Sacroiliitis proved by radiography or MRI
- HLA-B27 positivity plus clinical criteria

**Predominantly peripheral** (peripheral joint disease)
- with psoriasis
- with inflammatory bowel disease
- with preceding infection (reactive arthritis)
- other
Broader and more prevalent diagnostic entity
• well-established cause of chronic back pain
• estimated 1.0-1.5% of Caucasians (similar to RA)

Based on current progress:
• in the diagnosis of SpA
  – MRI-assisted detection of early inflammatory lesions in the spine and pelvis
  – established criteria for the recognition of “inflammatory back pain”

• in the understanding of SpA pathogenesis (unifying concepts)
  – experimental findings
  – shared success in therapies targeting TNF and IL-23/IL-17 axis
  – shared genetics (GWA studies)
Characteristics of Inflammatory Back Pain

- relatively young (age at onset <45 years)
- chronic duration (>3 months)
- insidious onset
- morning stiffness >30 min
- improvement with exercise / no improvement with rest
- nocturnal exacerbation (awaking from pain)
- alternating buttock pain
  - presence of ≥4 features: considered diagnostic
  - diagnostic sensitivity for axial SpA: 70-80%

Sieper et al., Ann Rheum Dis 2009, 68
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 feature of spondyloarthritis

- HLA-B27
  - plus
  - ≥2 other features of spondyloarthritis

Spondyloarthritis 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

Sensitivity: 82.9%  Specificity: 84.4%

*: radiography or MRI

Rudwaleit et al. Ann Rheum Dis 2009;68
Image from: Sieper and Poddubnyy, Lancet, 2017
Defining Outcomes in SpA:
DISEASE ACTIVITY & PROGRESSION EVALUATIONS

Objective measurements and questionnaires

• Disease activity:
  – BASDAI, ASAS, ASDAS, VAS of pain

• Function:
  – BASFI, BASMI, DFI, HAQ-S

• Global status:
  – BAS-G

• Radiological & MRI outcomes:
  – BASRI, mSASSS, ASspiMRI-a, ASspiMRI-c

Clinical remission:
- BASDAI <1.12 plus normal CRP or
- ASDAS (includes CRP or ESR) <1.3

LIMITATIONS
In patients with combined phenotype:
The well-validated parameters for axial disease may underestimate peripheral disease activity
**HLA-B27**

- The most important genetic risk factor (accounts for 40% of risk)
- Unclear role – several hypotheses
- Initially thought to present arthritogenic peptides to cytotoxic CD8 T-cells
- Experimental SpA in HLA-B27/hβ2m Tg rats
  - The absence of CD8+ T cells does not prevent disease
  - Germ-free state prevents gut and joint inflammatory disease (pathogen hypothesis)
- HLA-B27 homodimer formation leads to NK and killer T-cell activation
HLA-B27 misfolding hypothesis

HLA-B27 tends to misfold, resulting in high retention in the ER

- **HLA-B27 misfolding:**
  - initiates UPR (unfolded protein response; a cellular stress program)
    - triggers NFkB activation and production of proinflammatory cytokines
    - preferential induction of IL-23
      (which is high in AS patients and HLA-B27/hβ2m Tg rats)
  - associates with increased intracellular replication of Salmonella sp.
    (bacterial stress)
Current treatments

• Regardless of drug treatment and activity status: active exercise program is advised
  
• Non-steroidal anti-inflammatory agents (NSAIDs)
• Classic DMARDs
• TNF inhibitors
• IL-17 inhibitors
Current treatments

Non-steroidal anti-inflammatory agents (NSAIDs)
(including selective COX2 inhibitors)

• first-line drug treatment for pain and stiffness
  – continuous or on-demand
  – no particular NSAID is preferred in terms of efficacy

• risks of cardiovascular, gastrointestinal and renal adverse effects
  – no apparent difference between COX2-selective and non-selective NSAIDs
    (with the exception of naproxen)

Classic DMARDs (conventional synthetic; MTX, SSZ, LEF, CSA)

• generally not effective for axial SpA
• corticosteroids are not helpful
• have a role for peripheral arthritis
Usage of TNF-inhibitors upon failure of NSAIDs

Approval status for TNF-blocker treatment of axial SpA patients in the EU

From: Sieper and Poddubnyy, Lancet, 2017,
TNF inhibitors

Five TNF inhibitors (infliximab, etanercept, adalimumab, golimumab, and certolizumab)

- approved for ankylosing spondylitis and psoriatic arthritis
- also approved for non-radiographic SpA in EU (with the exception of infliximab)

• Good or very good improvement (for approx. 70% of patients)
  - all articular manifestations (axial disease, arthritis, enthesitis)
  - CRP levels
  - MRI-detectable inflammation in the sacroiliac joints or spine

• Better response:
  - active inflammation (CRP or active axial inflammation by MRI)
  - short disease duration or
  - young age

• Monoclonal anti-TNF antibodies (not etanercept) effective for:
  - active IBD
  - uveitis

• All treatments have demonstrated overall similar outcomes and safety profiles
  - most common adverse events being mild to moderate, non-serious infections

TNF inhibitors – unmet needs

• inefficacy in one-third of patients

• do not induce long-lasting remission
  – rapid relapse after tx interruption (in 75–90% of cases)

• appear to halt joint destruction, but fail to retard new bone formation (syndesmophyte growth)
  – bone remodelling may be independent from inflammation
Novel treatment options in SpA

- targeting IL-23/IL-17 axis pathway
- good rationale from experimental data

![Diagram showing the IL-23/IL-17 axis pathway involving Th17 cells, IL-17, IL-22, IL-23, and IL-23R. The role in autoimmune and autoinflammatory reactions is indicated.](image-url)
T-helper subsets

- Extracellular bacterial infections
- Fungal infections
- Autoimmunity
- Autoinflammation

- Extracellular parasites
- Asthma, allergy

- Antibody-mediated immunity
- Cell-mediated immunity and inflammation
- Intracellular pathogens (bacteria, viruses)
- Tumor surveillance
- Autoimmunity

- Lymphocyte homeostasis
- Immune tolerance
- Regulation of immune responses
Rationale for targeting IL-23/IL-17 axis pathway in SpA

- **Ankylosing spondylitis, psoriasis and Crohn's disease:**
  - are associated with a single nucleotide polymorphism of IL23R

- **HLA-B27 misfolding:**
  - initiates the unfolded protein response → increased IL-23 production

- **Patients with active ankylosing spondylitis:**
  - high IL-23 production by macrophages
  - increased numbers of circulating IL-23R+/IL-17 producing CD4 T-cells
    - memory TH17
    - Tγδ cells
    - particularly the KIR3DL2-expressing T-cells that respond to cell-surface HLA-B27 homodimers
  - In inflamed tissues (facet joints and synovium):
    - high IL-17 production by innate immune cells (neutrophils and mast cells) rather than T cells

- **IL-23 overexpression in mice:** induces enthesitis via IL-17 and IL-22 producing T cells
Biological disease-modifying drugs for targeting IL-23/IL-17 axis in SpA

IL-17 blockade

Secukinumab (anti-IL-17A mAb):

- approved for usage in **ankylosing spondylitis**, **psoriasis** and **psoriatic arthritis**
  - effective in psoriatic skin, enthesitis and dactylitis
  - also inhibits radiographic progression of peripheral arthritis

- effectiveness similar to TNF-blockers (no head-to-head trials so far)

However: need to be used with caution in **patients with coexisting Crohn’s disease** (serious exacerbations have been observed)
Biological disease-modifying drugs for targeting IL-23/IL-17 axis in SpA

**IL17-receptor blockade**

**Brodalumab** (mAb against receptors of IL17A, IL17F and IL23)

- approved for the treatment of *psoriasis*
- in psoriatic arthritis: moderate efficacy in a phase-2 RCT
- usage is linked to an increased risk of suicide

**IL-23 blockade**

**Ustekinumab** (anti-p40 subunit shared by IL-12 and IL-23):

- approved for usage in *psoriasis, active psoriatic arthritis* and *Crohn’s disease*
- good efficacy in a prospective open-label trial of AS patients
  — ongoing placebo-controlled trials in AS and non-radiographic axial SpA
Other biological disease-modifying drugs

Not effective in patients with SpA (in small prospective open-label trials)

- **Anakinra** (an interleukin-1 receptor antagonist)
- **Abatacept** (CTLA4-Ig; a T-cell modulator)
- **Rituximab** (anti-CD20; B-cell depleting mAb)
  - in psoriatic arthritis: moderate efficacy in a small exploratory evaluation

Not effective in placebo-controlled double-blind trials of AS patients

- **Tocilizumab and sarilumab** (anti-IL-6R mAbs):
  - Moderate or no efficacy of tocilizumab in patients with psoriatic arthritis in small exploratory evaluations
Tofacitinib (oral Janus kinase inhibitor)
  • in a placebo-controlled phase-2 study of AS patients:
    – fairly good clinical and MRI response

Apremilast (an oral PDE4 inhibitor; increases cAMP, resulting in decreased levels of proinflammatory cytokines)
  • in a placebo-controlled phase-2 trials:
    – non-efficacy in AS patients
    – moderate efficacy in psoriatic arthritis
Key messages

• SpA is a disease with heterogeneous manifestations that likely share several pathophysiologic pathways

• The targeting of the IL23/IL17 axis has emerged as a novel therapeutic option for SpA patients

• Valuable insights are expected from the investigation of biologic pathways associated with SpA including:
  – peptide handling prior to HLA presentation
  – innate and adaptive immune cell differentiation and activation
  – the microbiome and bacterial sensing in the gut
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