Spondyl(o)arthropathies - classification and management

Dr Gavin Clunie MD FRCP
Cambridge
2014
Spondylarthropathies

- Ankylosing spondylitis
- Axial SpA
- Psoriatic arthritis
- Reactive arthritis
- IBD-related. Enteropathic SpA (e.g. Crohn’s)
- Juvenile SpA
- *Seronegative enthesopathic/arthropathy syndrome*
- ?Enthesitis-related Arthritis (children)
- Undifferentiated spondylarthritis (USpA)
The spectrum of spondylarthropathy

Features
- HLA B27
- Uveitis
- Aortitis
- Urethritis
- IBD
- Psoriasis
Features of Spondyloarthritis

- MSK
- Inflammatory bowel symptoms
- Psoriasis

Time (years)

- Uveitis
Pattern of spondyloarthropathy

- Arthritis
- Inflammatory bowel symptoms
- Psoriasis

Time (years)
SpAs: Common immunopathological mechanisms: variable expression

Would allow for:

• varying features of a single AI process
• discordant symptoms temporally
• distinct clinical features
• subclinical ‘disease’
Ankylosing spondylitis

• Male preponderance
• Sacroiliitis
• Progressively stiffening spine
  – Vertebral squaring, syndesmophytes, discitis, enthesopathies and subenthesial osteitis
• Association with:
  – HLA B27
  – Uveitis
  – Peripheral joint synovitis/enthesitis
  – Inflammatory bowel (?clinically silent)
Sacroiliitis Grade 3 Bilaterally
HLA-B27 associated diseases

• Ankylosing spondylitis 95%

• Arthritis associated with inflammatory bowel disease 15%
  • with spinal disease (AS) 50%

• Psoriatic arthritis 20%
  • with spinal disease (AS) 50%

• Reactive arthritis (post infection)
  – mild 30%
  – severe (or progressing to AS) 75%
Peptide-Binding Groove of HLA-B27

Disease predisposing B27 subtype *04 differs just in positions 114 and 116 from non-predisposing subtype *06

What Is the Role of HLA-B27 in the Inheritance of Ankylosing Spondylitis?

- Only about 5% of B27-positive individuals develop AS.
- AS rarely recurs in families in the absence of HLA-B27, or in B27-negative members of AS-families.\(^1\)
- Twin and family studies suggest that about half of the risk of developing AS is due to HLA-B27.\(^{1,2}\)
- Thus B27 is almost essential for the inheritance of AS, but other genes determine which B27-positive cases develop the disease.

AS genetics

• AS is a polygenic disease!
• The protein encoded by ERAP1 is an aminopeptidase involved in trimming HLA class I-binding precursors so that they can be presented on MHC class I molecules. The encoded protein acts as a monomer or as a heterodimer with ERAP2
• ERAP1 has the 2nd strongest genetic association with AS after HLA-B27.
• HLA-B27 and ERAP1 are synergistic in susceptibility to both AS and psoriasis.
• ERAP1 variants alter peptide handling in the endoplasmic reticulum;
• Modulation of ERAP1 function has therapeutic potential in AS;
ERAP1 is only associated with HLA-B27 positive AS

Evans DM et al. Nat Genet 2011;43:761-7 (with permission)
Immunopathogenesis: AS theories

- B27+ selects and directs excessive antigen presentation;
- Non thymic deletion of self-reacting T cells;
- Abnormal processing of antigen (ERAP1);
- B27 as a recognised self peptide (heavy chain misfolding, x-reactive epitope, heavy chain recognition by NK cells);
Delay in diagnosis: 8.5-11 years
Delay in AS diagnosis

• Men don’t present to doctors;
• Back pain is often protocolised by Primary Care doctors;
• Hx of Inflammatory Back pain not taken
• Imaging for back pain is seldom done;
• Radiographic signs are late or subtle on conventional views;
• Radiological signs are not identified;
Inflammatory back (and neck) pain

- Chronic pain >3 months
- Morning stiffness >30 minutes
- Improvement with movement
- Disturbed sleep (second part of the night)
- Buttock pains (often alternating)

1:20 of back pain cases

Important to assess all patients with back pain accordingly, especially the young and middle aged.
ASAS classification criteria for axial SpA in patients with back pain for more than 3 months and age at onset less than 45 years


**ASAS classification criteria for axial spondyloarthritis (SpA)**
In patients with > 3 months back pain and age at onset <45 years

<table>
<thead>
<tr>
<th>Sacroiliitis on imaging*</th>
<th>Or</th>
<th>HLA-B27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plus</td>
<td></td>
<td>Plus</td>
</tr>
<tr>
<td>&gt;1 SpA feature#</td>
<td></td>
<td>&gt;2 other SpA features#</td>
</tr>
</tbody>
</table>

**SpA features**
- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn’s/colitis
- Good response to NSAIDs
- Family history of 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 modified NY criteria
Spectrum of Axial Spondyloarthritis

Patients with chronic back pain ≥3 months and aged <45 years

Axial SpA (ASAS criteria)

Non-radiographic stage
X-ray-negative

MRI positive sacroiliitis

MRI negative, HLA-B27-positive**

Ankylosing Spondylitis (modified New York criteria)

Radiographic stage
X-ray-positive sacroiliitis

Radiographic stage
X-ray-positive sacroiliitis and/or spinal changes***

* Heights reflect an estimate of the proportion of patients in each group
** Clinical arm if non-radiographic axial SpA
*** Radiographic evidence if inflammatory spinal changes including i.e., syndesmophytes, fusion or posterior element involvement
Anterior Longitudinal Ligament
Calcification in AS

Syndesmophyte
Marginal or paramarginal (eg DISH)
Link between spinal inflammation and new bone formation in AS

(n=39)

6.5 % (10 syndesmophytes developed from 153 VEs with inflammation)

2.1 % (16 syndesmophytes developed from 769 VEs without inflammation)

STIR MRI – inflammation at baseline

Syndesmophyte formation – after 2 years of anti-TNF

Baraliakos X, Arthritis Res Ther. 2008 Sep 1;10(5):R104
Enthesis: Definitions

• **An enthesis**: the attachment of ligaments or tendons to bone

• **Enthesopathy**: abnormal or pathological changes at an enthesis (includes enthesophytes)

• **Enthesitis**: inflammation at an enthesis. Imaged as inflammation and can be associated with osteitis or periostitis at adjacent bone
An Enthesis

Enthesis is a specialized site of connective tissue attachment to bone. It consists of cartilage, ligament, or capsule.
Entheses

• Are rich in fibrocartilage (FC), except some fibrous entheses – often insertion into diaphyseal periosteum
• FC forms in tendons and ligaments at sites of shear stress
• Entheses are often part of an ‘enthesis organ’ which includes tendon and periosteal FC, bursae, folds of synovium
Entheses are rich in fibrocartilage (FC), except some fibrous entheses – often insertional into diaphyseal periosteum. FC forms in tendons and ligaments at sites of shear stress.
ASAS/EULAR Recommendations for the Management of Ankylosing Spondylitis

- Education, exercise, physical therapy, rehabilitation, patient associations, self help groups

- NSAIDs
  - Axial disease
  - Peripheral disease
  - Sulfasalazine
  - Local corticosteroids

- TNF Blockers

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

---

ASSERT MRI Study: Example, Patient Before vs. After Therapy with Infliximab, STIR-Technique

Relapse after cessation of infliximab therapy

Baraliakos et al., J Rheumatol. 2007 Mar;34(3):510

Clinical relapse 41/42 pts

- partial remission
- BASDAI 50%
- ASAS 40%

weeks after Infliximab readministration

Clinical relapse 41/42 pts
Does spinal inflammation precede syndesmophytes and does anti-TNFα stop/reduce the process?

- There is a slightly increased probability of developing syndesmophytes in vertebral units with MRI-defined osteitis (OR 1.51 – 2.26)
- Growth of existing syndesmophytes at the vertebral level was not associated with osteitis
- The large majority of new syndesmophytes develop in vertebrae without inflammation
Does spinal inflammation precede syndesmophytes and does anti-TNFα stop/reduce the process?

- Results not consistent and well designed prospective studies done independently are lacking so the case for prevention has not been made.
Anti-TNFα-Therapy over 2 Years Does not Inhibit Radiographic Progression in AS

**Etanercept**

- mSASSS change:
  - Etanercept: 0.91
  - OASIS* all: 0.95
  - OASIS* meeting study entry criteria: 1.27

**Infliximab**

- mSASSS change:
  - Infliximab: 0.9
  - OASIS* all: 1.0
  - OASIS* meeting study entry criteria: 1.2

**Adalimumab**

- mSASSS change:
  - Adalimumab: 0.8
  - OASIS* all: 1.0
  - OASIS* meeting study entry criteria: 0.9

*OASIS=historical AS control group without anti-TNF therapy over 2 years
All comparisons p-value NS.

Other aspects of Anti-TNFα treatment in AS - summary

- Therapy is effective in (the ASAS 2009 definition of) Axial SpA;
- Treatment is safe long-term;
- Switching is a valid strategy for inefficacy on one agent;
- Remission following withdrawal of treatment does occur in some patients though predictors of remission are not known.
## Biologics other than TNFα Inhibitors and Small Molecules for AS Treatment

<table>
<thead>
<tr>
<th>Target</th>
<th>Targeting substance</th>
<th>Efficacy in AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cells</td>
<td>Rituximab (monoclonal antibody to CD20)</td>
<td>+/-</td>
</tr>
<tr>
<td>T-cells</td>
<td>Abatacept (inhibitor of T-cell co-stimulation)</td>
<td>-</td>
</tr>
<tr>
<td>Interleukin-1</td>
<td>Anakinra (IL-1 receptor antagonist)</td>
<td>-</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>Tocilizumab (monoclonal antibody to IL-6 receptor)</td>
<td>-</td>
</tr>
<tr>
<td>Interleukin-12/23</td>
<td>Ustekinumab (monoclonal antibody to p-40-chain IL-12/23)</td>
<td>+/-</td>
</tr>
<tr>
<td>Phosphodiesterase 4</td>
<td>Apremilast (PDE4 inhibitor, small molecule)</td>
<td>+/-</td>
</tr>
<tr>
<td>Janus kinase</td>
<td>Tofacitinib (JAK inhibitor, small molecule)</td>
<td>?</td>
</tr>
<tr>
<td>Interleukin-17</td>
<td>Secukinumab (monoclonal antibody to IL-17)</td>
<td>+</td>
</tr>
<tr>
<td>Interleukin-17</td>
<td>Ixekizumab (monoclonal antibody to IL-17)</td>
<td>?</td>
</tr>
</tbody>
</table>

+ effective as shown in randomized controlled trials, +/- there are some data on a positive effect from pilot trials, - not effective, ? no data available regarding efficacy

*Modified from:* Song IH and Poddubnyy D. Curr Opin Rheumatol 2011;23:346-51
Management of AS-aSpA

Overview

- **Exercise**
  - Can slow progression of spinal stiffness
  - Can address **fatigue** – poorly studied

- **Education**
  - About enthesitis; back care; exercise, NSAID use; occupational aspects; coping with fatigue

- **NSAIDs**
  - Reduce IBP and almost certainly don’t reduce bone changes

- **Injection of steroids for enthesitis**
  - Are useful for certain patients and may spare the use of DMARDs

- **DMARDs**
  - None have proved effective for spinal disease but are used for significant peripheral joint and/or enthesis disease

- **Surgery**
  - Rarely done but spinal osteotomy can correct severe kyphosis

- **Anti-TNFα**
  - All are effective for spinal and peripheral symptoms
  - ?variable / ? Lesser response of enthesitis

  **IL-17 pathway blocking** – efficacy unknown
Psoriatic arthritis - patterns

- Asymmetric oligoarticular pattern +/- spondylitis;
- Polyarticular pattern;
- DIPJ pattern with nail changes
- Arthritis mutilans (digit ‘telescoping’);
- Enthesopathy;
- Psoriatic arthritis-sine-psoriasis;

Patterns/features not exclusive simultaneously nor over time
Clinical patterns don’t segregate with genotypes

MSK lesions include: entheses, bone, synovium, tendon

Fatigue – v common

Ps-disease may include skin, MSK and gut manifestations
Ps immunogenetics

The immunogenetics of Psoriasis: A comprehensive review.

Harden JL, Krueger JG, Bowcock AM.

Abstract

Psoriasis vulgaris is a common, chronic inflammatory skin disease with a complex etiology involving genetic risk factors and environmental triggers. Here we describe the many known genetic predispositions of psoriasis with respect to immune genes and their encoded pathways in psoriasis susceptibility. These genes span an array of functions that involve antigen presentation (HLA-Cw6, ERAP1, ERAP2, MICA), the IL-23 axis (IL12Bp40, IL23Ap19, IL23R, JAK2, TYK2), T-cell development and T-cells polarization (RUNX1, RUNX3, STAT3, TAGAP, IL4, IL13), innate immunity (CARD14, c-REL, TRAF3IP2, DDX58, IFIH1), and negative regulators of immune responses (TNIP1, TNFAIP3, NFKBIA, ZC3H12C, IL36RN, SOCS1). The contribution of some of these gene products to psoriatic disease has also been revealed in recent years through targeting of key immune components, such as the Th17/IL-23 axis which has been highly successful in disease treatment. However, many of the genetic findings involve immune genes with less clear roles in psoriasis pathogenesis. This is particularly the case for those genes involved in innate immunity and negative regulation of immune specific pathways. It is possible that risk alleles of these genes decrease the threshold for the initial activation of the innate immune response. This could then lead to the onslaught of the pathogenic adaptive immune response known to be active in psoriatic skin. However, precisely how these various genes affect immunobiology need to be determined and some are speculated upon in this review. These novel genetic findings also open opportunities to explore novel therapeutic targets and potentially the development of personalized medicine, as well as discover new biology of human skin disease.
PsA PATHOPHYSIOLOGY

• Genetics
  – Association with MHC class I alleles, IL-1 cluster, TNF, IL-23R, and IL-12
  – IL-23R and HLA CW-6 have stronger links to PsA
  – MICA - A methionine/valine polymorphism at amino acid 129 of the major histocompatibility complex class I chain-related gene A (MICA-129) categorizes alleles into strong and weak binders of the natural killer (NK) and T-cell receptor NKG2D) stronger association with Ps vs PsA

• Aberrant bone remodeling
  – Overexpression of RANKL and increased levels of circulating OCP
  – Bone resorption triggered by TNFA
  – Increased pathologic bone formation linked to BMP expression and possibly the Wnt signaling pathway
Mechanisms of TNF-alpha- and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis.

Ritchlin CT, Haas-Smith SA, Li P, Hicks DG, Schwarz EM.

CD16 (FcRgammaII) as a potential marker of osteoclast precursors in psoriatic arthritis.

Chiu YG, Shao T, Feng C, Mensah KA, Thullen M, Schwarz EM, Ritchlin CT.
<table>
<thead>
<tr>
<th><strong>CASPAR criteria</strong> <em>(Specificity 0.987, sensitivity 0.914)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory articular disease (joint, spine, or entheseseal)</strong></td>
</tr>
<tr>
<td>With 3 or more points from the following:</td>
</tr>
<tr>
<td><strong>1. Current psoriasis (scores 2 points)</strong></td>
</tr>
<tr>
<td><strong>2. Personal history of psoriasis (if current psoriasis not present)</strong></td>
</tr>
<tr>
<td><strong>3. Family history of psoriasis (if personal history of psoriasis or current psoriasis is not present)</strong></td>
</tr>
<tr>
<td><strong>4. Psoriatic nail dystrophy</strong></td>
</tr>
<tr>
<td><strong>5. A negative test for rheumatoid factor</strong></td>
</tr>
<tr>
<td><strong>6. Current dactylitis</strong></td>
</tr>
<tr>
<td><strong>7. History of dactylitis (if current dactylitis is not present)</strong></td>
</tr>
<tr>
<td><strong>8. Radiological evidence of juxta-articular new bone formation</strong></td>
</tr>
</tbody>
</table>

**Genetics**
Strong linkage familial linkage
Susceptibility/disease expression loci: 16-25; many at 6p; most are IR-related
**Skin and Joints**

- 15 years before: 4
- 18 years before: 5
- 29 years before: 18
- 7 years before: 6
- 12 years after: 5
- 23 years after: 7

**Nails and Joints**

- 4 years before: 15
- 5 years before: 18
- 4 years before: 5
- 7 years before: 4
- 6 years after: 10
- 5 years after: 20
- 7 years after: 20

**Yrs. Before**

- + 20
- 10
- 18
- Synchr.
- 26

**Yrs. After**

- 10
- 20
Psoriatic arthritis - lesions

- Periosteal
  - New bone – syndesmophytes, enthesophytes, juxta-articular periosteal apposition
- Discitis
- Dactylitis
- Synovitis
- Enthesitis
  - Plantar fasciitis
  - Insertional Achilles Pain
  - Deltoid origin
  - Sacroiliitis and ileal rim enthesitis
  - Humeral epicondylitis and greater trochanter pain
  - Symphysitis
Knee synovitis in SpAs often associated with large volume effusions and thick synovial lining, often asymmetrical.
PsA therapeutics

- NSAIDs
- DMARDs therapy efficacy data is available but not high grade evidence for SZP, MTX, CYA
- Reasonable evidence is available for LEFLUNOMIDE (Arava)


Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial.

A randomized placebo-controlled trial of methotrexate in psoriatic arthritis.


Abstract

OBJECTIVE: MTX is widely used to treat synovitis in PsA without supporting trial evidence. The aim of our study was to test the value of MTX in the first large randomized placebo-controlled trial (RCT) in PsA.

METHODS: A 6-month double-blind RCT compared MTX (15 mg/week) with placebo in active PsA. The primary outcome was PsA response criteria (PsARC). Other outcomes included ACR20, DAS-28 and their individual components. Missing data were imputed using multiple imputation methods. Treatments were compared using logistic regression analysis (adjusted for age, sex, disease duration and, where appropriate, individual baseline scores).

RESULTS: Four hundred and sixty-two patients were screened and 221 recruited. One hundred and nine patients received MTX and 112 received placebo. Forty-four patients were lost to follow-up (21 MTX, 23 placebo). Twenty-six patients discontinued treatment (14 MTX, 12 placebo). Comparing MTX with placebo in all randomized patients at 6 months showed no significant effect on PsARC [odds ratio (OR) 1.77, 95% CI 0.97, 3.23], ACR20 (OR 2.00, 95% CI 0.65, 6.22) or DAS-28 (OR 1.70, 95% CI 0.90, 3.17). There were also no significant treatment effects on tender and swollen joint counts, ESR, CRP, HAQ and pain. The only benefits of MTX were reductions in patient and assessor global scores and skin scores at 6 months (P = 0.03, P < 0.001 and P = 0.02, respectively). There were no unexpected adverse events.

CONCLUSIONS: This trial of active PsA found no evidence for MTX improving synovitis and consequently raises questions about its classification as a disease-modifying drug in PsA. Trial registration. Current Controlled Trials, www.controlled-trials.com, ISRCTN:54376151.
Long Term Efficacy of TNF-Antagonists for the Treatment of Psoriatic Arthritis (ACR 20)

Infliximab\(^1\)

- Infliximab 5 mg/kg every 8 weeks

Etanercept\(^2\)

- Etanercept 25 mg BIW

Adalimumab\(^3\)

- Adalimumab 40 mg EOW

Weeks

n = 104  n = 87  n = 69  n = 205  n = 168  n = 148  n = 313  n = 269

# Dosage of TNFα-Blockers in AS, PsA and IBD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage AS</th>
<th>Dosage PsA</th>
<th>Dosage IBD</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>5 mg/kg</td>
<td>5 mg/kg</td>
<td>5 mg/kg</td>
<td>i.v. at week 0, 2, 6, q6 / q8*</td>
</tr>
<tr>
<td>Etanercept</td>
<td>25 mg</td>
<td>25 mg</td>
<td>Not used</td>
<td>s.c. twice weekly s.c. once weekly</td>
</tr>
<tr>
<td></td>
<td>50 mg</td>
<td>50 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40 mg</td>
<td>40 mg</td>
<td>40 mg</td>
<td>s.c. every 2 weeks**</td>
</tr>
<tr>
<td>Golimumab</td>
<td>50 mg</td>
<td>50 mg</td>
<td>Not used</td>
<td>s.c. every 4 weeks</td>
</tr>
</tbody>
</table>

* Psoriatic arthritis and inflammatory bowel disease (IBD)
** For IBD: initially higher dose
EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF PSORIATIC ARTHRITIS*

**Phase I**

- Adverse prognostic factors**
  (with or without major skin involvement)

  - Go directly to phase II (2)

- Major skin involvement
  (also in phase II-IV)

  - Consider consulting a dermatologist (C)

- Clinical diagnosis of active** psoriatic arthritis

  - Start non-steroidal antiinflammatory drugs (1)
    ± local glucocorticoid injections (4)

- Achieve target*** within 3-6 months

- No

  - Failure phase I: go to phase II

  - Yes

    - Continue

**Phase II**

- Contraindication for methotrexate

  - Lack of efficacy and/or toxicity in phase I
    (or adverse prognostic factors)

  - Predominantly axial disease or severe enthesitis

- Start leflunomide or sulfasalazine (2)
  (consider appropriate dose)

- Start methotrexate (2,3)

- Failure phase II: go to phase III

- Achieve target*** within 3-6 months

- No

  - No

    - Go directly to phase III (6,7,8)

    - Failure phase II: go to phase III

    - Achieve target*** within 3-6 months

    - Yes

      - Continue

    - No

      - Go directly to phase III (6,7,8)
PsA therapeutics: Biologics – what do we know?

- There are robust data for all anti-TNFα therapies for improving signs and symptoms of PsA;
- There is evidence for prevention of joint damage as early as 26 weeks
- There is limited evidence for strategies for switching for inefficacy though some patients do benefit
- There is class effect in causing ‘paradoxical Psoriasis’
PsA therapeutics: – what don’t we know?

• Do combination therapies have benefit over monotherapy?
• Do DMARDs and/or anti-TNFα therapy reliably suppress enthesis-predominant disease?
• Can DMARDs be withdrawn and patients remain in remission? Whom?
• Do we have reliable, validated and clinically relevant clinical outcome measures (eg inflammation markers, fatigue, imaging)?
• Does anti-TNFα switch on processes which may aggravate/cause Psoriasis and enthesitis?
Immunopathogenesis of psoriasis
IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+CD4−CD8− enthealse resident T cells.


Author information

Abstract

The spondyloarthropathies are a group of rheumatic diseases that are associated with inflammation at anatomically distal sites, particularly the tendon-bone attachments (entheses) and the aortic root. Serum concentrations of interleukin-23 (IL-23) are elevated and polymorphisms in the IL-23 receptor are associated with ankylosing spondylitis, however, it remains unclear whether IL-23 acts locally at the enthesis or distally on circulating cell populations. We show here that IL-23 is essential in entheses and acts on previously unidentified IL-23 receptor (IL-23R)+, RAR-related orphan receptor γt (ROR-γt)+CD3+CD4−CD8− stem cell antigen 1 (Sca1)+ entheseal resident T cells. These cells allow entheses to respond to IL-23 in vitro-in the absence of further cellular recruitment—and to elaborate inflammatory mediators including IL-6, IL-17, IL-22 and chemokine (C-X-C motif) ligand 1 (CXCL1). Notably, the in vivo expression of IL-23 is sufficient to phenocopy the human disease, with the specific and characteristic development of enthesitis and entheseal new bone formation in the initial complete absence of synovitis. As in the human condition, inflammation also develops in vivo at the aortic root and valve, which are structurally similar to entheses. The presence of these entheseal resident cells and their production of IL-22, which activates signal transducer and activator of transcription 3 (STAT3)-dependent osteoblast-mediated bone remodeling, explains why dysregulation of IL-23 results in inflammation at this precise anatomical site.
Anti-IL17 and IL-23/12 therapies

- Advances mainly in IL-17 and IL-23/IL-12 as therapy targets.

Ustekinumab is licensed for use in PsA though not authorised in UK (£10-20k [37-74k BRL]; NICE Final Appraisal Determination, March 2013)
<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab</td>
<td>IL-6 receptor</td>
<td>IL-6 receptor blockade</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>p40 subunit of IL-12/23</td>
<td>Blocks IL-23/T_{h}17 pathway</td>
</tr>
<tr>
<td>Apremilast</td>
<td>PDE4</td>
<td>Blocks cytokines and immune response</td>
</tr>
<tr>
<td>Anti–IL-17 Ab</td>
<td>IL-17A</td>
<td>Blocks IL-17A actions</td>
</tr>
<tr>
<td>Anti–IL-22 Ab</td>
<td>IL-22</td>
<td>Inhibits cell proliferation</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>JAK</td>
<td>Suppresses cytokine signaling</td>
</tr>
<tr>
<td>Denosumab</td>
<td>RANKL</td>
<td>Inhibits bone resorption</td>
</tr>
</tbody>
</table>

IL, interleukin; T_{h}, helper T cell; PDE, phosphodiesterase; Ab, antibody; JAK, Janus kinase; RANKL, receptor activator of nuclear factor-κB ligand.
Reactive arthritis

- Triggered by specific gut or genito-urinary infections
- Joint symptoms appear 1-3 week later
- Most cases resolve quickly but a proportion evolve into chronic spondyloarthropathy (AS)
Shortlist of SpA ReA-associated bacteria

- Salmonella
- Campylobacter - jejuni and coli
- Yersinia - enterocolitica and pseudotb.
- Shigella - flexneri, sonnei, dysentereri, boydii
- Chlamydia - trachomatis and pneumoniae
- Clostridium difficile
Post-infectious arthritis

- Post viral arthritis e.g. Parvovirus
- Post streptococcal arthritis
  - rheumatic fever
  - arthritis alone
- Post *Neisseria* arthritis
- Lyme disease
- Whipple’s disease

- *none of these are spondyloarthropathies*
Reiter’s syndrome??

- Reiter not first to describe the syndrome – thought it was due to a spirochaete
- Questionable subsequent career

- Often used as synonymous with sexually acquired ReA, but originally an enteric ReA
Incidence

- Chlamydia ReA - 46/million [Oslo]
- Enteric orgs ReA - 50/million [Oslo]
- Shigella ReA - 1.3/million [Finland]
  - ? 30/million exposed
- Campylobacter ReA - 43/million [Finland]
Forms of reactive arthritis

• “Rheumatologic” – presenting to secondary care
  – Inflammatory oligoarthritis + IBP involvement

• Milder disease – seen in primary care or non-presenting
  – Peripheral arthritis/enthesitis + back ache (IBP)
  – Self limiting
Clinical features for early Campylobacter-induced ReA

- 80% peripheral arthritis
  - 10% mono, 40% oligo, 50% poly
- 20% inflammatory back pain
- age 45 (20-74); 75% female; no children
- Onset 12 days (1-55)
- Duration: 50% 1 month; all <6 months
Enthesitis (Insertion of Achilles Tendon at Calcaneus) Right Heel
ReA management

• Diagnosis
• Education, NSAIDs
• Steroids if acute and severe
• IA steroid if joint-focal (rule out infection and consider crystal arthritis if aspirating joint)
• Sulfasalazine for persistent disease though MTX also used;
• TNFi for recalcitrant cases ?PsA ?aSpA
Rationale for antibiotic therapy in ReA

• bacterial infection persists and bacteria/antigens reach the joint
• pro-inflammatory T cells recognize these antigens
• antibiotics should speed antigen clearance

Trial antibiotics Reactive arthritis: Ciprofloxacin: 3 months

• Asymmetric arthritis + enteritis/urethritis
• 36 active : 35 placebo; < 3 months disease
• 25% B27+; most enteric (54, 22 culture +ive; 3 CT)
• no difference in any 1° endpoint ESR, joint count, global VAS, remission
• active group may be worse more i-a steroids (96 vs 62 injections)more DMARDs (8 vs 3) ~70% remission at 1 year
SpAs: summary

• SpAs are common (overall 2-3%; vs RA <1%)
• SpAs cause IBP and bone lesions
• B27 associated – variably depending on subclassification
• SpAs can relapse and remit through life and may be subtle in their effects
• PsA clearly a complicated disease clinically and in terms of genetic predisposition
• Respond to NSAIDs
• DMARDs not effective in spinal inflammatory disease all but only in peripheral disease
• Anti-TNFα effective in all and effective in treating axial and peripheral disease
• IL-23/Th17 axis blocking is a developing and key therapeutic area
Summary

• The classification of SpAs has evolved in recent years and has/will expand our ability to study and treat the wider SpA disease phenotype, and earlier;

• NSAIDs, DMARDs and Anti-TNF therapies, though effective for symptoms in AS/axial SpA have yet to show robust evidence for reducing spinal bone proliferation over time;

• Therapeutic studies have yet to show the most effective and cost efficient combinations of treatments in PsA, though the future is promising (with cheaper!) anti Il-23 and Il-17 biologics