Annual Rheumatology & Therapeutics Review for Organizations & Societies
Spondyloarthritis and Biologics: Update on Ankylosing Spondylitis & Psoriatic Arthritis—Guidelines and Management
Spondyloarthritis

• A family of related diseases that cause inflammation in spine, peripheral joints, and tendon/ligament insertion sites (enthesium)

• Spondyloarthritis includes:
  – Psoriatic arthritis
  – Ankylosing spondylitis
  – Undifferentiated spondyloarthritis
    • (axial spondyloarthritis, peripheral spondyloarthritis)
  – Reactive arthritis
  – Inflammatory bowel disease associated arthritis
Differences Between Psoriatic Arthritis (PsA) and Rheumatoid Arthritis (RA)

- PsA is an inflammatory joint disease with marked phenotypic diversity
  - Musculoskeletal features
  - Cutaneous
  - Gastrointestinal
  - Ocular manifestations

- Comorbidities
  - Obesity
  - Type 2 diabetes
  - Hypertension
  - Cardiovascular disease
  - Mortality
Important Characteristics of PsA

- Psoriasis precedes inflammatory joint disease in 70 to 85% of patients
- Equally common in men and women
- Reported prevalence of inflammatory joint manifestations among patients with psoriatic skin lesions varies widely
  - 6.25% (2000 US study) to 48% (2002 Swedish study)
  - Estimated at 20-30%
- Worldwide prevalence of PsA 0.03 to 1%
- Familial and genetic considerations
Synovio-entheseseal complex (SEC) Concept
Enthesitis

- Subchondral bone inflammation and resorption
- Periosteal new bone formation

Psoriasis and PsA: Shared Pathways

- Infiltrating leukocytes and their cytokine products may be similar in the skin and in the inflamed joint.

Image taken from AbbVie Presentation AHD-5019B.
PsA is initiated by immune response that may arise in the skin or possibly the process of skin and joint involvement may be triggered by an overlapping mechanism.

Role of Osteoclast Precursors

- Circulating osteoclast precursors (OCPs) have been shown to be elevated in PsA.
- OCPs drop rapidly after anti-TNF Rx
- 25% of patients with psoriasis had elevated OCPs and 50% of these developed PsA in 3 yrs
- Cell based assay difficult
The New Axial and Peripheral Spondyloarthropathy Criteria
In patients with ≥3 months back pain and age at onset <45 years

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

**HLA-B27 plus**
- ≥2 other SpA 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

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ASAS Classification Criteria for Peripheral SpA

Arthritis, Enthesitis, or Dactylitis, *plus*:

- ≥1 classic SpA feature:
  - Uveitis
  - Psoriasis
  - Colitis
  - Preceding infection
  - HLA-B27
  - Sacroiliitis by imaging*  
    * Definite radiographic sacroiliitis
    * Active (acute) inflammation on MRI

- ≥2 other SpA features:
  - Arthritis
  - Enthesitis
  - Dactylitis
  - History of inflammatory back pain
  - Positive family history

Psoriatic Arthritis
# CASPAR Criteria for PsA

## Established Inflammatory Articular Disease (joint, spine, or entheseseal) with 3 or more of:

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Psoriasis</td>
<td></td>
</tr>
<tr>
<td>(a) Current (2 pts)</td>
<td>Psoriatic skin or scalp disease as judged by a physician</td>
</tr>
<tr>
<td>(b) Hx</td>
<td>A history of psoriasis that may be obtained from patient, family doctor, dermatologist or rheumatologist</td>
</tr>
<tr>
<td>(c) Family Hx</td>
<td>A history of psoriasis in a first or second degree relative according to patient report</td>
</tr>
<tr>
<td>2. Psoriatic Nail Changes</td>
<td>Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination</td>
</tr>
<tr>
<td>3. A negative test for RF</td>
<td>By any method except latex, preferably by ELISA or nephelometry, according to local laboratory reference range</td>
</tr>
<tr>
<td>4. Dactylitis</td>
<td></td>
</tr>
<tr>
<td>(a) Current</td>
<td>Swelling of an entire digit</td>
</tr>
<tr>
<td>(b) Hx</td>
<td>A history of dactylitis recorded by a rheumatologist</td>
</tr>
<tr>
<td>5. Radiographic evidence of juxta-articular new bone formation</td>
<td>Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of hand or foot</td>
</tr>
</tbody>
</table>

Psoriatic Arthritis: Epidemiology

- Reported incidence of PsA varies from 3.4 to 8 per 100,000 population
- Present in about 20%-30% of patients with psoriasis
- Occurs in about equal numbers in both sexes
- Mean onset of symptoms: between ages 30 and 50
Characteristics of PsA (MRI)

Dactylitis

Enthesitis Linked to Bone Marrow Edema

## Treatments for PsA

<table>
<thead>
<tr>
<th></th>
<th>Peripheral Arthritis</th>
<th>Skin and Nail Disease</th>
<th>Axial Disease ¹</th>
<th>Dactylitis</th>
<th>Enthesitis</th>
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</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-articular steroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topicals</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Physiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psoralen UVA/UVB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral DMARDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biologics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Data drawn from AS trials (applied as surrogate for PsA spondylitis)

GRAPPA PsA Rx Recommendations

Peripheral arthritis
- Initiate therapy: NSAID
- IA steroids
- DMARD (MTX, CsA, SSZ, LEF)
- Biologics (anti-TNF)

Skin and nail diseases
- Initiate therapy: Topicals
- PUVA/UVB
- Systemics (MTX, CsA, etc)
- Biologics (anti-TNF, etc)

Axial disease
- Initiate therapy: NSAID
- PT
- Biologics (anti-TNF)

Dactylitis
- Initiate therapy: NSAID
- Injection
- Biologics (anti-TNF)

Enthesitis
- Initiate therapy: NSAID
- PT
- Biologics (anti-TNF)

Reassess response to therapy and toxicity

## Historical Data on MTX use in PSA

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Treatment</th>
<th># pts</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984 Willkens</td>
<td>3mo</td>
<td>MTX vs Placebo</td>
<td>37</td>
<td>Improved Physician Global Only</td>
</tr>
<tr>
<td>1995 Spadaro</td>
<td>12 mo</td>
<td>MYX vs Cyclosp</td>
<td>35</td>
<td>No def benefit</td>
</tr>
<tr>
<td>2005 Fraser</td>
<td>12 mo</td>
<td>MTX + placebo or Cyclo in non-resp</td>
<td>72</td>
<td>No def benefit</td>
</tr>
<tr>
<td>2008 Scarpa</td>
<td>6 mo</td>
<td>Early PSA</td>
<td>35</td>
<td>Definite Improvement</td>
</tr>
<tr>
<td>NOR-DMARD Lie</td>
<td>6 mo</td>
<td>Compared RA to PSA</td>
<td>430</td>
<td>Similar results</td>
</tr>
</tbody>
</table>
MTX in PsA: RESPOND Trial

- Open label, 16 week trial of MTX 15-20 mg/week vs. MTX plus infliximab

115 subjects randomized

57 assigned to IFX + MTX
10 discontinued
- 7 – Aes
- 1 – lost to follow up
- 2 – noncompliance

47 completed study through week 16

58 assigned to MTX alone
4 withdrew consent prior to treatment
7 discontinued
- 2 – Aes
- 3 – noncompliance
- 2 – protocol eligibility

47 completed study through week 16

Greater response to infliximab, however MTX effective

**Response at Week 16**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IFX + MTX (%)</th>
<th>MTX (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 50</td>
<td>100</td>
<td>80.0</td>
<td>0.0059</td>
</tr>
<tr>
<td>PASI 75</td>
<td>97.1</td>
<td>54.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PASI 90</td>
<td>70.6</td>
<td>28.6</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**MTX in Psoriatic Arthritis (MIPA) Trial**

**Hypothesis:** Methotrexate improves disease activity and function in psoriatic arthritis  
**Design:** 6-month RCT comparing methotrexate with placebo

- **Inclusion**  
  - Synovitis in ≥ 1 joint  
  - Psoriasis skin/nails

- **Exclusion**  
  - Other arthropathies  
  - Recent steroids/DMARDS  
  - Contra-indications to MTX

- **Intervention**  
  - Methotrexate (target 15mg/wk)  
  - Matching placebo

- **Primary outcome**  
  - Psoriatic Arthritis Response Criteria

- **Secondary outcomes**  
  - Patient Global Assessments  
  - Assessor Global Assessments  
  - HAQ & Pain  
  - Tender & Swollen Joint Counts  
  - ESR & CRP  
  - Composite Measures (ACR20)

Kingsley et al., *Rheumatology* 2012;51:1368.
MIPA Flowchart

**Screened**
- **462**

**Randomized**
- **221**

**Allocated to Active**
- **109**

Follow Up
- Lost to followed up (21)
  - Adverse Events: 5
  - Worse disease: 3
  - Patient choice: 13

Discontinued Intervention (14)
  - Adverse Events: 4
  - Worse disease: 7
  - Patient choice: 3

Analysed
- Intention to Treat: 109 (100%)
- Valid Complaint Completer: 67 (61%)
- Excluded from analysis: (7)

**Allocated to Placebo**
- **112**

Follow Up
- Lost to followed up (23)
  - Adverse Events: 4
  - Worse disease: 7
  - Patient choice: 12

Discontinued Intervention (12)
  - Adverse Events: 3
  - Worse disease: 7
  - Patient choice: 3

Analysed
- Intention to Treat: 112 (100%)
- Valid Complaint Completer: 61 (54%)
- Excluded from analysis: (16)

**Not Entered**
- **241**

Ineligible: 148
  - Previous methotrexate: 69
  - Inactive arthritis: 47
  - Concomitant disease: 21
  - Diagnostic uncertainty: 11

Non-consent: 93

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Kingsley et al., *Rheumatology* 2012;51:1368.
MIPÁ Results

- **Joint Counts, ESR and HAQ**

![Graphs showing Swollen Joint Count, Tender Joint Count, ESR, and HAQ over time for Methotrexate and Placebo treatments.](image)

Kingsley et al., *Rheumatology* 2012;51:1368.
MIPA Trial Caveats

- Small numbers of patients with high dropout rate – may have been inadequately powered
- Target dose of MTX was 15 mg/week – too low?
- Mean joint count ~5 – to few to identify response?
- Very high placebo response

Does MTX really work in PSA? Can we even tell from the available data?

Kingsley et al., *Rheumatology* 2012;51:1368.
PsA: Etanercept Phase III Endpoints

$P \leq 0.001$ for all endpoints

PsA: Etanercept Phase III +/- MTX

With MTX
- Placebo: 19%
- Etanercept: 62%

Without MTX
- Placebo: 13%
- Etanercept: 58%

*P ≤ .001

PsA: Adalimumab Phase III

PsA: Adalimumab Phase III PASI

Week 12

- Placebo: 15/69 (22%)
- Adalimumab 40 mg eow: 72/69 (105%)

Week 24

- Placebo: 12/69 (18%)
- Adalimumab 40 mg eow: 75/69 (109%)

All results P<0.001 placebo vs adalimumab

PsA: Infliximab Phase III ACR20

Primary Endpoint

- Week 14: Placebo 11%, Infliximab 58%
  - p < 0.001

Major Secondary Endpoint

- Week 24: Placebo 16%, Infliximab 54%
  - p < 0.001

PsA: Infliximab Extension

- Methods: Pts randomized to inflix 5 mg/kg every 8 wks through week 46
  - Open-label extension gave inflix 5 mg/kg at wks 54, 62, 70, 78, 86, 94
  - Open arrows = placebo infusions; filled arrows = infliximab infusions
- Conclusions: Infliximab therapy through week 94 resulted in sustained improvement in joint/skin sx, and inhibited radiographic progression

PsA: Infliximab Phase III PASI

Major Secondary Endpoint

Proportion of Subjects Achieving PASI 75

Week 14

- Placebo: 2.3%
- Infliximab: 63.9%
p < 0.001

Week 24

- Placebo: 1.1%
- Infliximab: 60.2%
p < 0.001

PsA: Infliximab Phase III Enthesitis

PsA: Infliximab Phase III Dactylitis

PsA: Golimumab Phase III Controlled and OL

**ACR 20**

- Week 24: 12 (n=146) vs 52* (n=113)
- Week 104: 72 (n=70) vs 91 (n=61)

**ACR 50**

- Week 24: 4 (n=140) vs 32* (n=105)
- Week 104: 51 (n=70) vs 66 (n=61)

**ACR 70**

- Week 24: 19 (n=140) vs 1* (n=105)
- Week 104: 44 (n=70) vs 31 (n=61)

**Enthesitis score†**

- Week 24: -13 vs 46* (n=70)
- Week 104: 40 vs 61 (n=61)

*p<0.001 vs PBO

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PsA: Certolizumab Phase III

**ACR 20**

- Week 12:
  - PBO: 24
  - CZP 200 mg Q2 weeks: 58
  - CZP 400 mg Q4 weeks: 52
- Week 24:
  - PBO: 24
  - CZP 200 mg Q2 weeks: 64
  - CZP 400 mg Q4 weeks: 56

**ACR 50**

- Week 12:
  - PBO: 11
  - CZP 200 mg Q2 weeks: 36
  - CZP 400 mg Q4 weeks: 25
- Week 24:
  - PBO: 13
  - CZP 200 mg Q2 weeks: 44
  - CZP 400 mg Q4 weeks: 28

**ACR 70**

- Week 12:
  - PBO: 3
  - CZP 200 mg Q2 weeks: 25
  - CZP 400 mg Q4 weeks: 13
- Week 24:
  - PBO: 4
  - CZP 200 mg Q2 weeks: 28
  - CZP 400 mg Q4 weeks: 24

*P* < 0.001 both CZP arms vs placebo.

PsA: Certolizumab PASI 75 Response

Week 24

CZP 200 mg Q2 weeks
CZP 400 mg Q4 weeks

Patients (%)

15
61
62

PBO
CZP 200 mg Q2 weeks
CZP 400 mg Q4 weeks

*P<0.001 CZP arms vs placebo.

Mease P, et al. EULAR 2012
Impact: Infliximab in PsA – Mean PASI Score at Week 98

PASI (Psoriasis Area and Severity Index) Score measured at baseline and weeks 50 and 98 for 46 patients evaluated at baseline and week 98.

IMPACT 2 – Total vdH-Sharp Score in PsA: Mean Change at Weeks 24 and 54

In placebo-controlled trial, pts received infliximab at wks 16, 18 and 22, then every 8 wks
All pts received infliximab from week 24

IMPACT 2 – Probability of Structural Change

Probability Plot

Change in total modified vdH-Score

Cumulative percentage

Patients with $\geq 1$ Dactylitis Digits or Enthesopathy at Baseline and at Week 24

$P<0.001$

$P=0.002$

ADEPT Study Design

- Co-primary endpoints included ACR20 response at Week 12 and mean change from baseline in mTSS for adalimumab at Week 48 vs. placebo at Week 24

EOW = every other week

*315 patients were initially randomized, although 2 patients did not receive study drug

Adalimumab in PsA (ADEPT): 2-Year ACR and PASI Scores

Adalimumab in PsA: (ADEPT): Mean Change From Baseline in Modified Total Sharp Score (mTSS) at 48 Weeks

*P ≤ 0.001 adalimumab at wk 24 vs placebo

Mease PJ et al. Poster FRI0212 presented at EULAR, June 2005; Vienna, Austria.
GO-REVEAL: ACR Response and Enthesitis Score (50 mg dose): Placebo Controlled at Week 24 and OL at Week 104

**ACR 20**

- Week 24: n=146, 12% ACR 20
- Week 104: n=70, 52% ACR 20

**ACR 50**

- Week 24: n=105, 4% ACR 50
- Week 104: n=70, 51% ACR 50

**ACR 70**

- Week 24: n=140, 19% ACR 70
- Week 104: n=61, 1% ACR 70

**Enthesitis score†**

- Week 24: -13
- Week 104: 61

RAPID- PSA: PASI 75 Response

PASI 75

Week 24

P<0.001 CZP arms vs placebo.

Mease P, et al. EULAR 2012 #512
GO-REVEAL: Mean Change From Baseline In Total vdH-S Score Over Time

- PBO/PBO to 50 mg (n=113)
- GLM 50 mg (n=146)
- GLM 100 mg (n=146)

*p=0.011; **p=0.086

RAPID™-PSA: ACR Response At Weeks 12 and 24

ACR 20

- Week 12:
  - PBO: 24%
  - CZP 200 mg Q2 weeks: 58%
  - CZP 400 mg Q4 weeks: 52%
- Week 24:
  - PBO: 24%
  - CZP 200 mg Q2 weeks: 64%
  - CZP 400 mg Q4 weeks: 56%

*P<0.001 CZP arms vs placebo.

ACR 50

- Week 12:
  - PBO: 11%
  - CZP 200 mg Q2 weeks: 36%
  - CZP 400 mg Q4 weeks: 25%
- Week 24:
  - PBO: 13%
  - CZP 200 mg Q2 weeks: 44%
  - CZP 400 mg Q4 weeks: 28%

ACR 70

- Week 12:
  - PBO: 3%
  - CZP 200 mg Q2 weeks: 25%
  - CZP 400 mg Q4 weeks: 13%
- Week 24:
  - PBO: 4%
  - CZP 200 mg Q2 weeks: 28%
  - CZP 400 mg Q4 weeks: 24%

Mease P, et al. EULAR 2012 #512
RAPID- PSA: PASI 75 Response

Patients (%)

Week 24

PASI 75

P<0.001 CZP arms vs placebo.

Mease P, et al. EULAR 2012 #512
IL-12 & IL-23 Differences: p40 Subunit is Common

Ustekinumab in PsA

- **PSUMMIT 1** – 615 pts with PsA despite DMARDs and/or NSAIDs
- **PSUMMIT 2** – 312 pts with PsA despite DMARDs, NSAIDs, and/or TNFi’s (or intolerance/toxicity from TNFi)
  - Intended as TNFi failure trial, but recruitment lagged
- Both included 3 arms:
  - Placebo
  - Ustekinumab 45 mg wks 0, 4, q12 wks
  - Ustekinumab 90 mg wks 0, 4, q12 wks
- Primary endpoints 24 weeks
PSUMMIT 1

Response at Week 24

PSUMMIT 2: Response at Week 24

*P≤.001 vs placebo; †P<.05 vs placebo.

Ritchlin C, et al. ACR 2012, #2557
Apremilast

- Inhibits PDE 4 conversion of cAMP to AMP
- ↑ cAMP leads to dis-inhibition of PKA
- Results in inhibition of NFkB and stimulation of CREB (Activates Transcription)
Role of PDE4

de Castro Barbosa, et al. BJPS 2011; 162:1674–1685
Apremilast PALACE Pivotal Trials

Response at Week 16

- PBO +/- DMARDs (n=168): 19 patients (ACR 20), 6 patients (ACR 50), 1 patient (ACR 70)
- Apremilast 30 mg BID +/- DMARDs (n=168): 16 patients (ACR 20), 4 patients (ACR 50), 1 patient (ACR 70)
- PBO +/- DMARDs (n=159): 19 patients (ACR 20), 5 patients (ACR 50), 1 patient (ACR 70)
- Apremilast 30 mg BID +/- DMARDs (n=162): 11 patients (ACR 20), 1 patient (ACR 50), 1 patient (ACR 70)
- PBO +/- DMARDs (n=169): 18 patients (ACR 20), 8 patients (ACR 50), 2 patients (ACR 70)
- Apremilast 30 mg BID +/- DMARDs (n=167): 41 patients (ACR 20), 15 patients (ACR 50), 4 patients (ACR 70)

Otezla® Package Insert
ACR20 Response Over 52 Weeks: PALACE 1, 2, 3  
Apremilast 30 mg BID

Patients Receiving Apremilast From Baseline Data as Observed

### ESTEEM: Apremilast Psoriasis

**LOCF, Full Analysis Set (N=844)**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo</th>
<th>Apremilast 30 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 75</td>
<td>5.3</td>
<td>33.1</td>
</tr>
<tr>
<td>PASI 50</td>
<td>17.0</td>
<td>58.7</td>
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<tr>
<td>sPGA</td>
<td>3.9</td>
<td>21.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 75</td>
</tr>
<tr>
<td>PASI 50</td>
</tr>
<tr>
<td>sPGA</td>
</tr>
</tbody>
</table>

*n = 282, 562*

Reich K, et al. AAD 2013: Late breaker.
Apremilast Dose Escalation Schedule

Table 1: Dosage Titration Schedule

<table>
<thead>
<tr>
<th>Day 1 AM</th>
<th>Day 2 AM</th>
<th>Day 2 PM</th>
<th>Day 3 AM</th>
<th>Day 3 PM</th>
<th>Day 4 AM</th>
<th>Day 4 PM</th>
<th>Day 5 AM</th>
<th>Day 5 PM</th>
<th>Day 6 &amp; thereafter AM</th>
<th>Day 6 &amp; thereafter PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
<td>30 mg</td>
<td>30 mg</td>
<td>30 mg</td>
</tr>
</tbody>
</table>

2.2 Dosage Adjustment in Patients with Severe Renal Impairment
T Cell Differentiation and Role of IL-17

Th 0
- IL-12/STAT4/T-bet
- IL-4/STAT6/GATA3

Th 1
- IL-12/STAT4/T-bet
- IL-23/STAT3

Th 2
- IL-4/STAT6/GATA3

Th 17
- IL-17
- TNFα
- IL-6
- IL-17F

IL-23/STAT3
- IL-23
- IL-4, IL-10

IFNγ
- IL-23

IL-17
- Cytokines/chemokines
- IL-1, -6, -8
- TNFα
- LIF, GRO, MIP-1α
- GM-CSF

Fibroblast
- IL-17

Macrophage
- IL-17

Chondrocyte
- IL-17

Osteoblast
- IL-17

Cytokines/chemokines
- destruction mediators
- MMPs
- Nitric oxide
- COX2
- RANK

Inflammation
- Cartilage damage
- Bone erosion

Osteoclastogenesis

Cytokine Signaling in PsA (and SpA)

Miossec P Nature Reviews Drug Discovery;2012(11):263
Secukinumab Phase III PsA

- Human anti-interleukin 17A antibody
- 2 pivotal trials, 1 IV load, 1 all subcut.
  - Doses 75 mg, 150 mg, 300 mg q4wks
- Primary endpoint 24 weeks
  - Open label extension to 52 weeks
Secukinumab Phase III, IV Load

- **Secukinumab 10/mg/kg IV → 150 mg subcut (n=202)**
- **Secukinumab 10/mg/kg IV → 75 mg subcut (n=202)**
- **Placebo (n=202)**

Responders (%)

**Week**
0 4 8 12 16 20 24 28 32 36 40 44 48 52

- 69.5%
- 66.9%
- 50.0%
- 50.5%
- 17.3%

Mease P, et al. ACR 2014, Boston, #953
Secukinumab Phase III, Subcut Only

Response at Week 24

McInnes I, et al. ACR 2014, Boston, #L1
Secukinumab Additional Endpoints

- Significant improvements in psoriasis, dactylitis, enthesitis in both trials
- Inhibition of structural damage demonstrated in IV load trial
- Significant, but lower response in TNFi experienced patients
- Safety:
  - SAE’s comparable to placebo
  - SIE’s 2.9/100 pt-yr 150 mg, 2.6/100 pt-yr 75 mg, 1.4/100 pt-yr placebo (IV load trial)
Ankylosing Spondylitis
Ankylosing Spondylitis (AS) Progression

### AS: Prevalence in Adults

<table>
<thead>
<tr>
<th>Ethnic Group or Region</th>
<th>Prevalence in General Population (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eskimos (Alaska)</td>
<td>0.4</td>
</tr>
<tr>
<td>Sami (Finland)</td>
<td>1.8</td>
</tr>
<tr>
<td>Northern Norway</td>
<td>1.4</td>
</tr>
<tr>
<td>Mordovia</td>
<td>0.5</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>0.2</td>
</tr>
<tr>
<td>Germany (Berlin)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Background: AS

• Common clinical features:
  – Axial arthritis (eg, spondylitis, sacroilitis)
  – Arthritis of “girdle joints” (shoulders, hips)
  – Morning stiffness
  – Fatigue
  – Fever
  – Weight loss

• Disease in many pts is progressive, may lead to disability

• Severe AS may be associated with CV disease, pulmonary fibrosis, or neurologic sequelae
Age at Onset of Symptoms and Age at Diagnosis in AS – Data from German AS Society (DVMB)

From first symptoms to diagnosis: 5 - 10 yrs


- **Clinical criteria:**
  - Low back pain and stiffness for more than 3 months. Improvements occur with exercise but not with rest
  - Limitation on motion of the lumbar spine (occurring in sagittal and frontal planes)
  - Limitation of chest expansion (relative to normal values)

- **Radiological criterion:**
  - Sacroiliitis (grade ≥2 bilaterally or grade 3-4 unilaterally)

---

Definite AS: Radiologic criterion present plus 1 or more clinical criterion

Probable AS: 3 clinical criteria present or radiologic criterion present without clinical criteria

---


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

NSAIDs

Axial disease

Peripheral disease

Sulfasalazine

Local corticosteroids

TNF antagonists

## Efficacy of NSAIDs and Cox II Inhibitors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pooled Effect Size* (95% CI)</th>
<th>NSAIDs</th>
<th>Coxibs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal pain</td>
<td>1.11 (0.96-1.26)</td>
<td>1.05 (0.88-1.22)</td>
<td></td>
</tr>
<tr>
<td>Peripheral joint pain</td>
<td>0.62 (0.26-0.97)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Function</td>
<td>0.62 (0.47-0.76)</td>
<td>0.63 (0.47-0.80)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: NSAIDs improve spinal pain, peripheral joint pain, and function; Coxibs are equally effective, although effect on peripheral arthritis has not been investigated.

*Compared with placebo, over 6 weeks

# 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

Response after 24 Weeks of TNF-alpha Blocker Treatment in Ankylosing Spondylitis

*Different studies, no head to head comparison

Long-Term Efficacy of Etanercept

72-Week Open-Label Extension
RCT
(25 mg BIW etanercept)

Open Label
(25 mg BIW etanercept)

% Responders

Week

Golimumab in AS: Week 104

• **Purpose**
  – To assess GLM efficacy and safety at week 104

• **Methods**
  – 356 pts randomized to GLM 50 mg, GLM 100 mg, PBO (1.8:1.8:1)
  – Primary end point at week 14 with early escape possible at week 16
  – Placebo pts crossed to GLM 50 mg at week 24
  – Patients receiving GLM 50 mg could be dose-escalated to 100 mg during f/u

• **Results (Week 104)**

<table>
<thead>
<tr>
<th></th>
<th>GLM 50</th>
<th>GLM 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>90</td>
<td>118</td>
</tr>
<tr>
<td>ASAS 20 (%)</td>
<td>77 (86)</td>
<td>91 (77)</td>
</tr>
<tr>
<td>ASAS 40 (%)</td>
<td>74 (82)</td>
<td>71 (60)</td>
</tr>
</tbody>
</table>

• **Conclusion**
  – Clinical improvements noted at week 24 persisted to week 104
  – No new safety signals
  – Patients who early-escaped from GLM 50 mg to GLM 100 mg at week 14 had a diminished response on all parameters, identifying a subset of patients who are TNF unresponsive?

Braun J et al. ACR 2009, Philadelphia #1259
Certolizumab in AS and Axial SpA

- RCT of pts meeting criteria for AS or non-radiographic axial SpA (without sacroiliitis on plain radiographs)
- 325 pts treated for 12 weeks with placebo, 200 mg q2 wks, or 400 mg q4 wks

- Equally effective in both classic AS and NR-axSpA

Adalimumab in Axial SpA

- RCT of 195 pts meeting criteria for axial SpA
- Treatment with placebo vs. adalimumab 40 mg eow

Apremilast pilot in AS

START Study Design
Pilot Study Investigating Co-primary Clinical and MRI Endpoints (N=38)

Active AS patients
Randomise
Placebo tablets BID

Apremilast tablets 10 mg BID, days 1-2
Apremilast tablets 20 mg BID, days 3-4
Apremilast tablets 30 mg BID, days 5-end

Follow-up

Screening 2 weeks
Dose 12 weeks
4 weeks

Clinical assessments
Days
1 8 15 29 57 85 113

Imaging assessments

Apremilast Results

IL-6 in AS

- No significant response to IL-6 inhibition in two separate trials:
  - Tocilizumab—99 pts 8 mg/kg IV q4 wks x 12 wks
  - Sarilumab (human anti-IL6R) — 100 pts 150 mg/kg subcut weekly x 12 wks
- No MRI improvement in sarilumab trial
- IL-6 doesn’t appear to be a viable target in AS
Secukinumab in AS

- Pilot study of secukinumab (human anti-IL17A) in 30 pts with AS
  - 2 mg/kg IV q3 wks x 2 doses
  - Primary endpoint at week 6

Percent Responding

<table>
<thead>
<tr>
<th></th>
<th>ASAS20</th>
<th>ASAS40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secukinumab</td>
<td>61%</td>
<td>30%</td>
</tr>
<tr>
<td>Placebo</td>
<td>17%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Baeten D, et al. ACR 2010, #L7
Secukinumab Phase III AS

• Human anti-interleukin 17A antibody
• 2 pivotal trials, 1 IV load, 1 all subcut
  – Doses 75 mg, 150 mg, q4wks
• Primary endpoint 16 weeks
  – Open label extension to 52 weeks
Secukinumab in AS, IV Load

• Similar response in all subcut trial, except 75 mg dose somewhat less effective
• Reduced efficacy in TNF experienced patients
• Safety profile similar to that seen in PsA

Baeten D, et al. ACR 2014, Boston, #819
Are TNFi ‘Disease Modifying’ in AS?

- TNFi do not prevent ‘osteoproliferation’ in established AS
- “Damage” in AS is both, ‘catabolic + anabolic’ (erosions + new bone formation)
- Could starting TNFi early (in ‘nr axial SpA’ stage) prevent osteoproliferation?
- Do they reduce rate of erosion progression?

<table>
<thead>
<tr>
<th></th>
<th>Change in mSASSS Over 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>0.9</td>
</tr>
<tr>
<td>Infliximab</td>
<td>0.9</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>0.8</td>
</tr>
<tr>
<td>OASIS</td>
<td>1</td>
</tr>
</tbody>
</table>

Three separate trials, not head-to-head

Do TNFi Slow Radiographic Progression in AS?

• Longitudinal cohort of 1600 patients with AS
• 368 with 2 radiographs at least 1.5 years apart (1.5−9 yrs) [mean = 2.8 yrs]
  − Mean disease duration 16.5 years (±12.9 years), 75% male, 83% B27+
• Baseline ESR, baseline mSASSS & smoking associated with progression in MVA

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline ESR</td>
<td>1.02</td>
<td>0.07</td>
</tr>
<tr>
<td>Baseline mSASSS</td>
<td>1.05</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.1</td>
<td>0.01</td>
</tr>
<tr>
<td>TNFi use</td>
<td>0.38</td>
<td>0.01</td>
</tr>
</tbody>
</table>

• Reliability of propensity modelling?
• Adjustment for timing of xrays?
• Controlled for NSAID use?

TNFi protective against progression

Haroon N & Gensler LS et al, ACR 2012, Washington, #782
Cannot Fully Withdraw TNFi Therapy in AS

Baraliakos X, et al. *EULAR* 2005, #FRI0222
Comcast Rx: Infliximab On-Demand

- 247 pts. randomized after loading to infliximab q6 wks vs. on-demand upon symptom recurrence
  - On-demand group then randomized to MTX up to 12.5 mg vs. no MTX.
  - Symptom recurrence determined via phone call
- ASAS 20 at 58 weeks 75% vs. 46%
- More infusions in continuous group
  - MTX did not affect response or number of infusions
- More patients with infusion reactions in continuous treatment group (14.5% vs. 6.5%).
- MTX - no impact.

Possibility of Reducing TNFi Dose in AS

- Retrospective - etanercept could be stretched out as far as 25 mg q12 days with maintenance of efficacy
- Prospective, open label trial from Italy - 78 pts in “clinical remission” (BASDAI < 4, no acute phase reactants or extra-axial disease) on etanercept 50 mg weekly were randomized to 50 mg q wk or eow
  - Nearly all pts maintained response, in both groups

Conclusions

- PsA, AS and other spondyloarthropathies are joint, enthesial, and skin inflammatory diseases with distinctive clinical presentations and extra-articular manifestations.

- Traditional DMARDs may be effective for peripheral disease, but no apparent effectiveness in axial disease.

- Current biologics may not slow progression, but there is interest in targets that may...
Conclusions (cont.)

- Anti-TNF agents have demonstrated efficacy for treating multiple clinical domains of PsA, AS, axial, and peripheral SpA
- Ongoing research is examining additional targets, such as IL-17, for treating incomplete responders to anti-TNF inhibitors
- The new axial and peripheral SpA criteria expand the patient base for whom emerging therapies will be assessed