Psoriatic Arthritis Update

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## Disclosures

<table>
<thead>
<tr>
<th>Consultant</th>
<th>Research</th>
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<tbody>
<tr>
<td>Abbott</td>
<td>Amgen</td>
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<td>Amgen</td>
<td>UCB</td>
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<td>Lilly</td>
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<td>Janssen</td>
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<td>Novartis</td>
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<td>Pfizer</td>
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Overview

Psoriatic arthritis and Axial SpA Updates

Pathogenesis
Clinical Perspectives
Emerging therapies
Treatment Recommendations
Treatment horizons

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Accelerated Drug Development in PsA

- **1973-2003**: Gold, Sulfa, MTX, HCQ, LEF
- **2003-2012**: TNFi
- **2013**: UST
- **2014**: APR
- **2015**: Sec*
- **2016-**: Ixe Brod Combo IL-23 IL-22
TNFi therapy in PsA: Phase III trials

Patients (%)
Pathogenesis
Genetic Risk Factors in PsA

HLA-B
IL-23R PsA specific
PTPN22
CD8+ memory T cells


Bowes J. Nature Comm. 2015
Genotype predicts phenotype

Joint deformities and ankylosis
B*08:01-C*07:01:01

Dactylitis
B*08-B*27

Enthesitis
B82705-C:01:07

Fitzgerald O. Arthritis Res Therapy 2015
T Cell Subsets in SpA
Lymphocyte populations in PsA synovial fluid

Menon B. Arthritis Rheum 2014

Leijten E. A & R 2015 online
Innate and adaptive lymphocyte subsets

Gasteiger G. Nat Rev Immuno 2014
IL-23 and resident T cells promote enthesitis and osteoproliferation

# IL-23/Th17 pathways in murine models

<table>
<thead>
<tr>
<th>Model</th>
<th>Manipulation</th>
<th>Skin/Nails</th>
<th>Joint</th>
<th>Enthesitis</th>
<th>Dactylitis</th>
<th>Ref</th>
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</thead>
<tbody>
<tr>
<td>DBA/1</td>
<td>Male/trauma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1,2</td>
</tr>
<tr>
<td>ZAP 70</td>
<td>Curdlan inj</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>2-4</td>
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<tr>
<td>K749 KI</td>
<td>Cross with K5.Stat.3C</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>5</td>
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<td>B10Q</td>
<td>Mannan inj</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</table>

Synovial Histopathology of PsA

SpA tissues (PsA, AS, USpA): more vascularity, neutrophil and CD 163+ macrophage infiltration

No citrullinated proteins in polyarticular PsA

Synovial histopathology of PsA (either oligo or poly) resembles other SpA subtypes more than RA.

Both groups can be differentiated from RA
What are the defining histopathologic features of RA and PsA?

- Power Doppler ultrasound biopsies performed on 32 PsA and 23 RA treatment naïve patients with arthritis for <12 months duration
- Patients were well matched on BL characteristics
- Gene expression of pro-inflammatory cytokines (TNFα, IL-1B, IL-6, IL-23, IL-17A, IL-12A) was comparable between PsA and RA

PsA synovial tissue has less T cell infiltration, lower synovitis scores, and a more fibroid pathotype than RA despite similar levels of cytokine gene expression, suggesting divergent disease pathways

Nerviani A et al. EULAR 2016, London, #FRI0442
Gene expression in PsA closer to psoriasis than other forms of arthritis

Clinical Perspectives
RAPID3 as a disease outcome measure in PsA

- Sub-analysis of Tight Control of Psoriatic Arthritis (TICOPA)

  - RAPID3 was highly correlated with PASDAS (Pearson correlation 0.794, P<0.01), responsive to change, and discriminated well between treatment groups
  - Little added value with inclusion of skin VAS (RAPIDPs) (Pearson correlation 0.831)

RAPID3 is a potentially valuable clinical response measure in PsA

Coates LC et al. EULAR 2016, London, #THU0419

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Patient Perspectives: MAPP Survey

Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) in US, Canada, Europe

3426 patients surveyed
21% psoriasis

Lebwohl M. JAAD 2014; May 2014
Undiagnosed Psoriatic Arthritis

Reich et al. 2008
Yang et al. 2011
Radtke et al. 2009
Ibrahim et al. 2009
Carneiro et al. 2012
Tinazzi et al. 2012
Haroon et al. 2012
Walsh et al. 2013
Marshall et al. 2010
Fernandez-Sueiro et al. 2012
Henes et al. 2011
Mease et al. 2013

Combined studies
15.5% 95CI [11.5-19.5]
I² = 96.86%

Vallani AP JADD 2015;73(2):243
Delay in Diagnosis >6 months

- Erosive Disease OR 4.6
- Deformed Joints OR 2.3
- Arthritis Mutilans OR 10.6
- Sacroiliitis OR 2.3
- Functional Disability OR 2.2
- Drug Free Remission OR 0.4

Courtesy of Laura Coates

Haroop M, et al. ARD 2014
Low correlation between psoriasis and PsA activity

New Therapies
Tight control of early PsA (TICOPA)

- 48 week UK multicenter, open-label RCT
  - 206 pts with early DMARD naive PsA (<24 months symptoms)
    - Median age 45, 52% male, 71% polyarthritis
- 1° outcome: ACR20 at 48 weeks
- Tight control (TC): 101 pts, q4 wk visits; MTX escalation to 25 mg targeting MDA, then combo DMARDs, then TNFi at 24 wks if ≥ 3 active joints (or alternative DMARD if not MDA but <3 active joints)
- Usual care: 105 pts, q12 Wk visits – no set protocol, limitations
- SAEs in 20 patients (14 TC, 6 usual care)

Tight control of PsA disease activity using a treat-to-target approach significantly improves joint and skin outcomes for newly diagnosed PsA pts

Coates L, Lancet 2015
TICOPA: Prescribed therapy at 12 and 48 weeks

Tight control: more combination therapy at 12 wks, more biologics by 48 wks

Coates L. Lancet online; Oct 2015
• 527 patients randomized to placebo, APR 30 mg BID, APR 20 mg BID\textsuperscript{1}
• 1\textsuperscript{o} endpoint: ACR20, Wk 16:
  – PBO 17%, APR20 29%, APR30 32%
• Most common AEs: URTI (3%) and nasopharyngitis (4%)
• SAEs in 5.2%

• 3-year integrated safety analysis of PALACE 1-3 – no new safety signals\textsuperscript{2}
• 1 withdrawal during Year 3 for diarrhea in APR20, none in APR30

• Sustained response in DMARD-naïve pts
• No new safety signals

1. Wells AF et al. EULAR 2016, London, #THU0422;
2. Mease PJ et al. Ibid, #THU0470
Targeting the IL-17 Pathway
SEC subcutaneous only in PsA: FUTURE 2

**TNFi-naïve (65% of pts)**

- 397 adults, active PsA, injections at baseline, Weeks 1, 2, 3, 4, then q4w

**TNFi-IR (35% of pts)**

Both doses effective. Consider 300 mg in TNFi-IR?

McInnes I Lancet 2015 386;9999:1137
SEC inhibits structural damage: FUTURE 1

- 606 adults with active PsA
- Higher rates of non-progression with SEC vs PBO
  - 75 mg, 92.3%
  - 150 mg, 82.3%
  - PBO, 75.7%
- Rate of non-progression maintained up to Week 52 and increased to 86.8% after rescue in PBO patients
SEC safety in PsA

- Integrated safety data from FUTURE 1 and 2, 974 patients
  - Mean exposure to SEC 358 days

<table>
<thead>
<tr>
<th>Safety outcomes (n/100 Pt-Y)</th>
<th>PBO-controlled phase (16 weeks)</th>
<th>Entire safety period</th>
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<tbody>
<tr>
<td></td>
<td>Any SEC, n=703</td>
<td>PBO, n=300</td>
</tr>
<tr>
<td></td>
<td>Patients, n (%)</td>
<td>Cases/100 patient-years, n (95% CI)</td>
</tr>
<tr>
<td>AEs</td>
<td>414 (59)</td>
<td>175 (58)</td>
</tr>
<tr>
<td>Candida</td>
<td>5 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>9 (1.3)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>SAEs</td>
<td>24 (3.4)</td>
<td>12 (4.0)</td>
</tr>
<tr>
<td>SIEs</td>
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*Includes patients from the PBO group re-randomized to SEC

- Anti-drug antibodies in 1 patient – no apparent loss of efficacy
- No signal of MACE or malignancy
- 1 new onset Crohn’s in SEC, 1 in PBO

Long-term safety and tolerability consistent with blinded data
Ixekizumab (IXE) in active PsA: 52-week results (NRI analysis)

ACR responders at Week 52

<table>
<thead>
<tr>
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<th>IXE 80 mg q4w (N=191)</th>
<th>IXE 80 mg q2w (N=190)</th>
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<tbody>
<tr>
<td>ACR20</td>
<td>67</td>
<td>53</td>
</tr>
<tr>
<td>ACR50</td>
<td>49</td>
<td>34</td>
</tr>
<tr>
<td>ACR70</td>
<td>34</td>
<td>35</td>
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PASI responders at Week 52

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<th>IXE 80 mg q4w (N=131)</th>
<th>IXE 80 mg q2w (N=117)</th>
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<tr>
<td>PASI 75</td>
<td>71 (59%)</td>
<td>59 (49%)</td>
</tr>
<tr>
<td>PASI 90</td>
<td>67 (56%)</td>
<td>67 (56%)</td>
</tr>
<tr>
<td>PASI 100</td>
<td>49 (56%)</td>
<td>56 (56%)</td>
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Complete resolution of enthesitis

<table>
<thead>
<tr>
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<th>IXE q4w (n=191)</th>
<th>IXE q2w (n=190)</th>
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<tbody>
<tr>
<td>N</td>
<td>115</td>
<td>101</td>
</tr>
<tr>
<td>Baseline</td>
<td>2.8</td>
<td>3.0</td>
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<tr>
<td>Change</td>
<td>-1.8</td>
<td>-1.6</td>
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Complete resolution of dactylitis

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<th>IXE q4w (n=191)</th>
<th>IXE q2w (n=190)</th>
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<tbody>
<tr>
<td>N</td>
<td>53</td>
<td>48</td>
</tr>
<tr>
<td>Baseline</td>
<td>84</td>
<td>74</td>
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<td>Change</td>
<td>-82</td>
<td>-62</td>
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AEs

<table>
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<tr>
<th></th>
<th>IXE q4w (n=191)</th>
<th>IXE q2w (n=190)</th>
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<tbody>
<tr>
<td>Any infection</td>
<td>53 (28%)</td>
<td>53 (28%)</td>
</tr>
<tr>
<td>Serious infection</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Any Candida infection</td>
<td>3 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>1 (0.5)</td>
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<tr>
<td>Cytopenias</td>
<td>6 (3)</td>
<td>4 (2)</td>
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<tr>
<td>Neutropenia</td>
<td>3 (2)</td>
<td>1 (0.5)</td>
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<tr>
<td>Cerebro-cardiovascular event</td>
<td>4 (2)</td>
<td>3 (2)</td>
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<tr>
<td>Malignancy</td>
<td>1 (0.5)</td>
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<tr>
<td>CD or UC</td>
<td>1 (0.5)</td>
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Mease PJ et al. EULAR 2016, London, #OP0109
IXE: Secondary outcomes at Week 52

Results sustained through 52 weeks, no apparent difference between doses

- MDA results similar whether using PGA or PASI for skin\(^1\)
- Improvements in function, QoL, work productivity\(^2\)
- IXE efficacy was not significantly affected by background DMARD use\(^3\)

2. Gottlieb A et al. Ibid, #THU0430;
3. Coates LC et al. Ibid, #THU0441
Bimekizumab proof-of-concept study in PsA

- Monoclonal antibody directed against both IL-17A and IL-17F
  - in vitro human assay showed additive effects of IL-17A and IL-17F inhibition
- 4 doses at 0, 3, 6 weeks c/w placebo, primary endpoint ACR-N at Week 8
  - 40, 80, 160, 320 mg iv, with double dose at baseline

ACR20, ACR50, and ACR70 through Week 8

- 100% PASI 75 at Week 8
- No significant safety signals. 3 SAEs in 1 pt related to a fall

Bimekizumab demonstrated high efficacy for skin and joints in and no major safety signals in this early proof-of-concept study in PsA
Brodalumab in PsA: 2-year results

- 156/168 patients (93%) entered 96-week open-label extension
  - Brodalumab 140 mg, 280 mg, or PBO in 12-week DB phase
  - Planned 280 mg dose reduced to 210 mg after protocol amendment

- Week 108:
  - 23 (15%) reported SAE
    - Most frequent SAEs (≥2 patients): coronary artery disease, cholelithiasis, cellulitis
    - AEs of special interest: 11 oral candidiasis, 1 neutropenia, 1 suicidal ideation
    - No deaths

Brodalumab remains effective at 2 years. Brodalumab was pulled from clinical trials due to reports of suicidal ideation and completed suicides

Mease P et al. EULAR 2015, Rome, #OP0175
Divergent tissue responses with IL-17i

Psoriasis

Papp K. NEJM 2014; 366(13):1181

PsA

Mease P. NEJM 2014;370(24):2295
In vitro data and In vivo models may not predict response in disease

Antagonism of IL-23/Th17 not effective in RA
IL-22 mAb not effective in psoriasis
IL-17 mAb worsened Crohn’s colitis

IL-17 null mice show increased periosteal bone formation

http://clinicaltrials.gov/show/NCT01645280
Heuber W. Gut 2012;61(12):1693
Treatment Recommendations
GRADE process for generating recommendations

Making recommendations
15. Going from evidence to recommendations—the meaning of strong and weak recommendations
16. Going from evidence to recommendations—determinants of a recommendation’s direction and strength
17. Going from evidence to recommendations—resource use

BMJ 2008;336;1049-1051
GRAPPA Treatment Recommendations for Psoriatic Arthritis 2015

**Methods**

- Updated systematic literature reviews performed based on data publicly available through November 2014.

- Six separate literature reviews completed covering Rx for key PsA clinical domains: Arthritis, Spondylitis, Enthesitis, Dactylitis, Skin and nail disease.

- Evidence assessed from the published literature reviews and formally evaluated with the GRADE system to provide treatment recommendations.

GRAPPA PsA Rx Recommendations 2015

Assess activity, impact and prognostic factors

Peripheral arthritis
- DMARDs (MTX, SSZ, LEF, TNFi, TNFi or PDE4)
- NSAIDs and/or corticosteroids as indicated
- Biologics (TNFi, IL12/23i, IL17i) or PDE4
- Switch Biologic (TNFi, IL17i) or PDE4

Axial Disease
- NSAIDs only
- Biologics (TNFi, IL12/23i, IL17i) or PDE4
- Switch Biologic (TNFi, IL12/23i or IL17i)

Enthesitis
- NSAIDs
- Biologics (TNFi, IL12/23i, IL17i) or PDE4
- Switch Biologic (TNFi, IL12/23i or IL17i)

Dactylitis
- NSAIDs
- DMARDs (MTX, LEF, SSZ) or PDE4
- Biologics (TNFi, IL12/23i, IL17i) or PDE4
- Switch Biologic (TNFi, IL12/23i or IL17i)

Skin
- Topicals (keratolytics, steroids, vit D analogues, emollients, calcineurin inhibitors)
- Phototherapy (TNFi, IL12/23i, IL17i) or PDE4
- Biologics (TNFi, IL12/23i, IL17i, Actizin)

Nails
- Topical or Procedure or DMARDs (CSA, LEF, MTX, Actizin)
- Biologics (TNFi, IL12/23i, IL17i) or PDE4
- Switch Biologics (TNFi, IL12/23i, IL17i) or PDE4

Which domains are involved?

Consider previous therapy, patient choice, other disease involvement and comorbidities. Choice of therapy should address as many domains as possible.

Treat, periodically re-evaluate and modify therapy as required.

2015

Coates L et al. ACR 2015 San Francisco # Late Breaker Poster

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Treatment Horizons
Targeting IL-12 and IL-23

Patel D. Immunity 43, December 15, 2015
SpA therapy: Novel strategies

Systemic therapies for psoriasis patients with arthritis markers
Early dx of PsA
Stratification biomarkers
Antibody to IL-17A and F
Innate lymphocytes?
IL-23 as a target
Combination therapies: biologics (TNF, IL-17, IL-23)
Bitypical antibodies
Life-style modification
IL-17R blockade- next steps??
Take Home Points

1. PsA: Shared disease pathways and mechanisms with psoriasis

2. IL-23/IL-17 and TNF pathways of critical importance

3. Targeting IL-17 is an effective strategy in psoriasis and PsA

4. New therapies targeting IL-17 A/F & IL-23 promising
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R Thiele
S Haas-Smith

Dongee Li
Anatole Kleiner
Debbie Campbell
S Moorehead

B Marston
R Barrett

NIH A1078907, AR54041, RRF, Amgen