Gaps in the Treatment of Psoriasis and PsA for Systemic Therapy

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Disclosure

Mark Lebwohl is an employee of Mount Sinai which receives research funds from: Abbvie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen / Johnson & Johnson, Kadmon, Medimmune/Astra Zeneca, Novartis, Pfizer, Valeant and ViDac.

Dr. Lebwohl is also a consultant for Allergan, Aqua Leo-pharma, and Promius.
Research gaps in psoriasis: opportunities for future studies


Psoriasis outcome measures: a report from the GRAPPA 2012 annual meeting

Gottlieb AB, Armstrong AW.
J Rheumatol. 2013;40:1428-33
Research Gaps

• Can we predict who’ll develop PsA and can we prevent it?
• Can we predict who’ll develop other comorbidities (cardiac, renal, etc) and can we prevent them?
• Can we predict who’ll respond to which therapy?
Can we predict who’ll develop PsA?

*(Can we treat to prevent joint disease?)*
Patient perspectives in the management of psoriasis: Results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey.

139,948 households were screened and 3426 patients
prevalence of psoriasis/PsA ranged from 1.4% to 3.3%
79% had psoriasis alone and 21% had PsA
27% (psoriasis) and 53% (PsA ± psoriasis) of patients rated it as severe
45% had not seen a physician in a year;
Psoriasis and Psoriatic Arthritis: Timing of Onset

- Psoriasis 1st: 72%
- Arthritis 1st: 21%
- Concurrent: 7%
Subclinical Joint Involvement in Patients With Psoriasis

- Joint structural damage can occur before the appearance of clinical symptoms of PsA
- In a study by Offidani and colleagues, which used MRI rather than conventional radiography to assess joint involvement, 68% of patients with psoriasis were found to have 1 or more arthritic signs
  - Appeared before patients experienced clinically evident joint symptoms
  - Joint damage was only detected by X-ray imaging in 32% of these patients

Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis.
van der Heijde DM, et al

Figure 1. Sites evaluated for radiographic evidence of erosions (●) and narrowing (I) in the hands and feet of patients with early rheumatoid arthritis.
Etanercept for Psoriatic Arthritis: Radiographic Improvement

*X-rays of hands and wrists (includes DIP joints); **P = .0001 vs placebo (stratified rank test). †Start of OLE.

Adalimumab for Psoriatic Arthritis: Radiographic Results

*Mean Change in mTSS Through Week 48

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Baseline</th>
<th>24 Wk Mean Change</th>
<th>48 Wk Mean Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>152</td>
<td>21.8</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>144</td>
<td>23.7</td>
<td>−0.1*</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*p ≤ .001 vs placebo for ranked ANCOVA.

Total vdh-S Score – Mean Change from Baseline at Week 24*

*Median Change in both groups was 0.0

Treatment of psoriatic arthritis with tumor necrosis factor inhibitors: longer-term outcomes including enthesitis and dactylitis with golimumab treatment in the Long term Extension of a Randomized, Placebo-controlled Study (GO-REVEAL).

Kavanaugh A, Mease P.

Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA)


PALACE 1: Apremilast in PsA (Phase 3)

- Apremilast, oral phosphodiesterase 4 (PDE4) inhibitor
- RDBPC trial stratified for DMARD use, N=489, 1:1:1 randomization
- Major adverse events diarrhea and nausea, resolve over time

Change From Baseline in Modified Total vdhS Score Over Time (ITT)

Mean Change from Baseline

Week 0  Week 24  Week 52

- Placebo (n=310)
- Placebo→45 mg at Wk 24 (n=269)*
- UST 45 mg (n=308)
- UST 90 mg (n=309)

*Patients who did not receive UST are excluded
FUTURE 1: Radiographic progression in PsA patients stratified by MTX use

Baseline to Week 24 (full analysis set)

<table>
<thead>
<tr>
<th>Pooled SKB doses</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>0.08</td>
</tr>
<tr>
<td>MTX: Yes</td>
<td>0.57</td>
</tr>
<tr>
<td>MTX: No</td>
<td>0.58</td>
</tr>
</tbody>
</table>

*P<0.05 vs PBO
Change in mTSS >0.5 considered progression of radiographic disease

Gottlieb AB, et al. EADV 2015, P0348 Sponsored by Novartis Pharma AG
Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1.

Mease PJ, et al
Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Mease PJ et al; Ann Rheum Dis 2017;76:79-87.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>IXEQ4W</th>
<th>IXEQ2W</th>
<th>Adalimumab 40 mg Q2W*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>106</td>
<td>107</td>
<td>103</td>
<td>101</td>
</tr>
<tr>
<td><strong>LS mean change from baseline mTSS (SE)</strong>†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 16</td>
<td>0.36 (0.07)</td>
<td>0.13 (0.07)§</td>
<td>0.06 (0.07)§</td>
<td>0.12 (0.08)§</td>
</tr>
<tr>
<td>Week 24</td>
<td>0.49 (0.09)</td>
<td>0.17 (0.08)§</td>
<td>0.08 (0.08)§</td>
<td>0.10 (0.09)§</td>
</tr>
<tr>
<td>Percentage of patients with change in mTSS at week 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0</td>
<td>72.0</td>
<td>83.0</td>
<td>83.5</td>
<td>91.6</td>
</tr>
<tr>
<td>≤0.5</td>
<td>77.4</td>
<td>89.0**</td>
<td>94.8↑</td>
<td>95.8↑</td>
</tr>
<tr>
<td>≤0.95</td>
<td>83.9</td>
<td>94.0‡</td>
<td>98.9§</td>
<td>95.8§</td>
</tr>
</tbody>
</table>
Brodalumab Phase 2 PsA study: Clinical response and improvement in psoriasis in subjects with PsA

Mease P, et al. AAD 2014, P7605
We don’t have a serologic marker that predicts psoriatic arthritis or its severity
Research Gaps

• Can we predict who’ll develop PsA and can we prevent it?
• Can we predict who’ll develop other comorbidities (cardiac, renal, etc) and can we prevent them?
• Can we predict who’ll respond to which therapy?
Risk of myocardial infarction in patients with psoriasis.

Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB.

JAMA 2006;296:1735-41
Does treatment of psoriasis reduce the risk of cardiovascular disease?
Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register.

Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis.

Wu JJ, Poon KY, Channual JC, Shen AY

Research Gaps

• Can we predict who’ll develop PsA and can we prevent it?
• Can we predict who’ll develop other comorbidities (cardiac, renal, etc) and can we prevent them?
• Can we predict who’ll respond to which therapy?
Cost of Biologics: Year 1

- Etanercept: ~$79,623
- Adalimumab: ~ $69,670
- Ustekinumab: ~$52,525-105,015
- Infliximab: ~$22,995-80,482 (50-100 kg q4-8w. at 5mg/kg)
- Secukinumab: ~$75,007
- Ixekizumab:~$82,891
- Brodalumab:~$31,395
- Guselkumab: ~$71,237

www.goodrx.com 1/21/18
ERASURE study results: Secukinumab rapidly improved plaque Ps, and sustained high responses through 52 weeks

- **PASI 75 Response**: 87.8% improvement in PASI 75 response at Week 12 for SEK 150 mg group.

- **SEK 300 mg (n=245)**
- **SEK 150 mg (n=245)**
- **Placebo (n=247)**

*P<0.0001 vs placebo at Wk 12. Grey arrows indicate peak response

**IGA score of 0 (clear) or 1 (almost clear) and an improvement of at least 2 points on the IGA scale compared with baseline;**

**One subject did not sign informed consent before starting study procedures and was excluded from analyses**

ERASURE study results: Secukinumab rapidly improved plaque Ps, and sustained high responses through 52 weeks


*\( p < 0.0001 \) vs placebo at Wk 12

\( ^{a} \)IGA score of 0 (clear) or 1 (almost clear) and an improvement of at least 2 points on the IGA scale compared with baseline;

\( ^{b} \)One subject did not sign informed consent before starting study procedures and was excluded from analyses

BRODALUMAB

PASI 75 Response Rate (NRI) by Week in the Induction Phase

Data on file, Amgen.
BRODALUMAB

PASI 90 Response Rate (NRI) by Week in the Induction Phase

Data on file, Amgen.
PASI 100 Response Rate (NRI) by Week in the Induction Phase

Data on file, Amgen.
Figure 2. Time Course of Clinical Responses as Measured by the Psoriasis Area and Severity Index (PASI) and Static Physician’s Global Assessment (sPGA) through 20 Weeks, According to Study Group.

Shown are the percentages of patients who had reduction in the PASI score by at least 75% (Panel A), at least 90% (Panel B), and 100% (Panel C), respectively. Panel D shows the percentage of patients who had an sPGA score of 0 (clear of disease) or 1 (minimal disease). Asterisks indicate significant differences (P<0.05) between each study group and placebo. Missing data were imputed by the last-observation-carried-forward method. Similar results were found with the use of nonresponse imputation (data not shown).
PASI 50 at Wk 4 optimal for predicting PASI 75 at Wk 12

- Good overall sensitivity (83%), specificity (87%), positive predictive value (90%), and negative predictive value (77%)
- Combining results for 75 and 150 mg groups showed similar results
- PASI 50 responders at Wk 4 were called early responders

Zhu B, et al. EADV 2012: P952
Early responders had significantly higher improvement in PASI 75 and 100 than non-responders (p<0.05; **p<0.01; ***p<0.001 vs non-responder group).

Zhu B, et al. EADV 2012: P952

**IXEKIZUMAB**
Week 16 Partial Responders (50 ≤ PASI < 75) and Nonresponders (25 ≤ PASI < 50) That Achieved PASI 50, 75, or 90 at Week 28

<table>
<thead>
<tr>
<th></th>
<th>UST Combined*</th>
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<tbody>
<tr>
<td></td>
<td>50 ≤ PASI &lt; 75 at Week 16</td>
</tr>
<tr>
<td>Patients at Week 16, n</td>
<td>98</td>
</tr>
<tr>
<td>Achieve PASI 50 at Week 28</td>
<td>98%</td>
</tr>
<tr>
<td>Achieve PASI 75 at Week 28</td>
<td>52%</td>
</tr>
<tr>
<td>Achieve PASI 90 at Week 28</td>
<td>13%</td>
</tr>
</tbody>
</table>

USTEKINUMAB

Successful treatment of recalcitrant palmoplantar psoriasis with etanercept.
Successful treatment of hand and foot psoriasis with infliximab.
Di Lernia V, Guareschi E.

Severe psoriasis pustulosa palmaris et plantaris (Barber-Königsbeck) treated successfully with soluble tumour necrosis factor receptor fusion protein (etanercept).
Kasche A, et al
Safety and efficacy of Adalimumab in the treatment of moderate to severe palmoplantar psoriasis: an open label study.

Richetta AG, et al

4/11→clear
5/11→50% improvement
Increased expression of IL-17A and limited involvement of IL-23 in patients with palmo-plantar (PP) pustular psoriasis of PP pustulosis; results from a randomized controlled trial.
Bissonnette R et al.

- UST 45mg doesn’t work
Investigator-initiated, open-label trial of ustekinumab for the treatment of moderate-to-severe palmoplantar psoriasis.

J Dermatolog Treat. 2012 May 8. [Epub ahead of print]

7/20 → clear (90 mg:6/9; 45mg:1/11)
12/20 → >2point PGA approval
An investigator-initiated, open-label study evaluating the efficacy and safety of UST in patients with moderate-to-severe palmar/plantar psoriasis

- 24 subjects with palmar/plantar psoriasis with PGA ≥3 treated with FDA-approved dose of UST using weight-based dosing
- Report of 20/24 subjects, 11 in 45-mg dose, 9 in 90-mg dose. Mean weight of subjects not reported.
Apremilast, an oral phosphodiesterase-4 inhibitor, in the treatment of palmoplantar psoriasis: Results of a pooled analysis from phase II PSOR-005 and phase III Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) clinical trials in patients with moderate to severe psoriasis.

Bissonnette R, et al.

PPPGA 0 or 1 Achievement at Week 16 in Patients With Baseline PPPGA ≥3

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Apremilast 30 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSOR-005</td>
<td>20.0</td>
<td>66.7</td>
</tr>
<tr>
<td>ESTEEM 1</td>
<td>30.8</td>
<td>38.6</td>
</tr>
<tr>
<td>ESTEEM 2</td>
<td>31.3</td>
<td>65.4</td>
</tr>
</tbody>
</table>

*P<0.05 vs. placebo.

Includes patients with Palmoplantar Psoriasis Physician Global Assessment (PPPGA) ≥3, indicating moderate or severe palmoplantar psoriasis, at baseline; all data are last observation carried forward. n/m=number of patients with response/number of patients with sufficient data for evaluation.
Clinical and patient-reported improvements of hand and/or foot psoriasis with ADA 40 mg qow: Subanalysis of REACH

- Subanalysis of REACH study looking at elements of erythema, scaling, induration and fissuring (ESIF) score along with DLQI

Menter A, et al. AAD 2012: P5061; Study sponsored by Abbott Laboratories
Secukinumab shows significant efficacy in palmoplantar psoriasis: results from GESTURE, a randomized controlled trial.


Secukinumab 300 mg (n = 69)
Secukinumab 150 mg (n = 68)
Placebo (n = 68)

ppPASI % change from baseline

Week

-80 -70 -60 -50 -40 -30 -20 -10 0

-4.0%
-35.3%
-54.5%
More than Half of All Subjects on Secukinumab 300 mg Achieved Clear/Almost Clear Palms and Soles at 1.5 Years

Palmoplantar disease improved by approximately 70% at 1.5 years in subjects receiving secukinumab 300 mg
UNCOVER-3: Ixekizumab in patients with palmoplantar involvement: ppPASI 75 response rates

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo/IXE q4w (n=20)</td>
<td>80.0</td>
</tr>
<tr>
<td>IXE q4w/IXE q4w (n=32)</td>
<td>71.1</td>
</tr>
<tr>
<td>IXE q2w/IXE q4w (n=38)</td>
<td>68.8</td>
</tr>
<tr>
<td>ETN/IXE q4w (n=25)</td>
<td>80.0</td>
</tr>
<tr>
<td>Placebo washout</td>
<td>80.0</td>
</tr>
</tbody>
</table>

- These patients have plaque psoriasis of the hands and feet, this does not address efficacy in pustular disease nor patients with predominantly palmoplantar disease.

Menter A, et. al. EADV 2016, FC03.08; Sponsored by Eli Lilly and Company